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DIGITALIS AND OTHER CARDIOTONIC DRUGS

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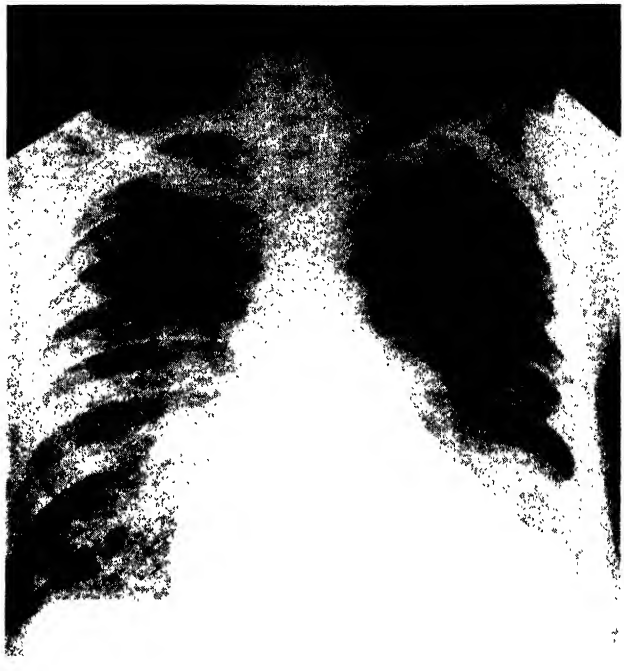
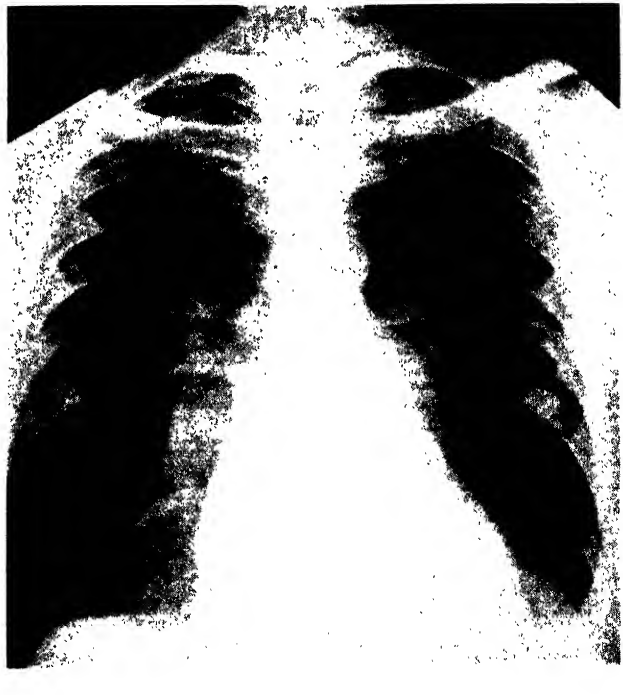


A 6 ft. x-ray film of the chest of a 46-year-old man with rheumatic heart disease, mitral stenosis, auricular fibrillation, and congestive failure.



B. AFTER ORAL ADMINISTRATION OF FULL DOSES OF CEDILANID. NOTE DIMINUTION OF CARDIAC SILHOUETTE.

OXFORD MEDICAL PUBLICATIONS

DIGITALIS

AND OTHER CARDIOTONIC DRUGS

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AFFECTIONATELY
TO MY WIFE
JENNIE

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Preface to the Second Edition

THE need for keeping pace with the newer developments concerning digitalis and the warm reception accorded this book have prompted the publication of a second revised edition.

Recent experimental and clinical research with digitalis, and more specifically the cardiac glycosides, has added much to our knowledge of the mechanisms of action of this group of drugs, although the subject is still controversial. The relative values of the results obtained in the laboratory and those obtained in the clinic are often controversial in any field of investigation, and this is particularly true in the study of the pharmacological action of digitalis. At any rate, whatever be the significance of observations that can now be made with improved techniques in humans, a great debt is owed the pharmacologist, physiologist, and chemist for their contributions which constitute a basis for clinical study.

Catheterization of the heart has made possible a more direct and accurate evaluation of the effect of digitalis on the circulation in man. The cardiac output is measured most accurately by direct application of the Fick principle. This has been done for many years in experimental laboratories, samples of mixed venous blood being obtained by direct puncture of the right cardiac chambers — a procedure impractical in human subjects because of the dangers associated with direct needle puncture of the heart. The advent of venous catheterization has made the application of the direct Fick principle possible in man. The same procedure has enabled investigators to obtain direct records of the alterations in the atrial pressure as conditioned by various physiological functions as well as by the administration of drugs such as digitalis.

The classical studies of Starling on the heart-lung preparation have

demonstrated a relationship between the cardiac output of the heart and the venous pressure, leading to the conclusion that the output of the heart is essentially dependent on venous return. Certain observations with cardiac catheterization on human subjects have tended to render support to this concept, whereas other investigators have discovered a number of circumstances in which venous pressure and cardiac output could not be correlated. Thus, it has become apparent that the regulation of the cardiac output in the human is more complex than is the case in the heart-lung preparation. The application of venous catheterization to the study of heart failure has also led to the discovery that low cardiac output is not present consistently in all instances of congestive heart failure and that under certain circumstances the cardiac output, in fact, may be increased. The latter condition apparently prevails when there is a disproportion between demand for oxygen and its supply. In addition, the theory of Starling concerning the pathogenesis of heart failure does not any longer reign supreme, since newer findings have provided a different explanation for the manifestations of cardiac insufficiency. All these discoveries may have some bearing both on the pharmacological actions of digitalis and its clinical application. It is hoped that the new data incorporated in the current edition will aid the reader in orienting himself with respect to these recent developments.

In the postwar period many additional studies have been made on the clinical application of cardiac glycosides. These have been incorporated in the present volume and, generally speaking, the text has been brought up to date.

The author wishes to acknowledge the many courtesies of the publishers, who have helped to make the revision of this work possible.

E. R. M.

Preface to the First Edition

THE literature on digitalis is voluminous but there seems to be a definite need for a treatise which, under one cover, includes not only past achievements but in addition the newer findings, with particular emphasis upon the pure cardiac glycosides that are proving to be so important in the management of heart disease.

In the last century our medicaments consisted almost exclusively of natural substances. The minerals were generally in the form of salts; the organic medicines were principally dried herbs and perhaps purified extracts of vegetable or animal origin. As is evidenced today, chemistry and related sciences are the foundation of medicine and one cannot dispute the important role chemistry plays in influencing medical thought and in developing new medicinal agents. This trend is also apparent in the development of cardiac drugs.

The isolation of the chemically pure glycosides from cardiac glycoside-bearing plants by Stoll, Jacobs, Smith, and their collaborators represents notable achievements in pharmaceutics. About two decades ago Hatcher prophesied that 'Every discovery of a method for the preparation of a pure principle of this type helps to a better understanding of the way to use these drugs. Such work must eventually lead to the employment of one of the pure principles in the place of the many crude digitalis bodies now employed.' We may see this prophesy fulfilled within the life span of the present generation.

It is hoped that all those who are called upon to treat heart disease may find this small volume helpful.

Material in this monograph has been freely drawn from the literature, including illustrations, and grateful acknowledgment is given to the authors.

I am indebted particularly to Professor William Dock for his criti-

cism of the manuscript; to my wife for her encouragement and careful proofreading; to Mr. Harry Althouse for his valuable help in compiling the bibliography, and to Mrs. Jean Lee and Mrs. May Shaw for assistance in the preparation of the manuscript.

The opinions set forth in this book are strictly those of the author and do not represent the views or policies of the Department of Medicine and Surgery, Veterans Administration.

E. R. M.

Foreword

THE history of the cardiotonic glucosides shows cycles of abuse and neglect, and with each new pharmacologic observation of a property of the drug, new claims arise about how the agent acted in heart failure. Slowing of the pulse, rise in blood pressure (in the dog), systolic arrest of the heart (in the frog), atrioventricular block, decrease in cardiac output (in the dog) — each in turn has been hailed as *the* action on which the therapeutic effects must depend. Pharmacologists were slow in proving that digitalis, almost without effect on the contractions of the normal mammalian ventricle, nevertheless acted in striking fashion to shorten systole, increase the efficiency and diminish fatigue-like changes in the damaged ventricle, whether in the isolated papillary muscle, the heart-lung preparation, or in several of the types of congestive failure in man. They were even slower in making available pure principles, so that these bodies, like morphine, quinine, and other active plant ingredients, could be given in purified uniform preparations at negligible cost.

In this account of our present knowledge of the digitalis bodies and other cardiotonic agents, Dr. Movitt has made available detailed recapitulations of the chemical, pharmacologic, and clinical behavior of a varied and extremely important group of drugs. This is knowledge which will refresh the minds of men who have recently finished their training, and much of it may be new to those who have not paid close attention to this field of medical literature. It is noteworthy that the fundamental chemical and pharmacologic literature has been so fully reviewed, for even doctors whose chemistry is rusty and whose contact with the laboratory is remote need to be aware of the activity which has led to the recent changes in digitalis preparations available for clinical use, and it is only by seeing the structural formulae, read-

ing of the analytical work, and being made conscious of the agreements and disagreements of the specialists that they can appreciate how progress has been made and what lies behind the therapeutic methods of progressive students of heart disease.

While totally dissimilar in chemical and in pharmacological properties, digitalis is much like the Minot fraction of liver so far as its place in medicine is concerned. The crude natural sources were revealed by sagacious clinical observation, the chemistry of the essential fractions long defied the labors of the best investigators, and relatively crude preparations continued in use long after highly concentrated forms were known. Little used in pediatrics, both are invaluable in specific disorders most common in the middle-aged and elderly. The exact nature of the dysfunction for which digitalis is a specific is not understood, but it seems to be a functional failure, often associated with aging and involution; the exact dysfunction in pernicious anemia is also unknown, but it certainly is one of the involutional disorders. One course of liver extract, or of digitalis, may suffice to restore a sick person to a feeling of complete well-being, but relapses are to be expected sooner or later, and most of those benefited by these agents finally learn that a regular ration is as essential as food and drink. Indeed, for the patient who develops myocardial failure, without any myocarditis, endocrine disorder or vitamin deficiency, digitalis therapy is much like supplying a specific hormone. However, the effects are quickly apparent, and the final failure of the heart to respond, after months or decades of effectiveneess, recalls the occasional development of refractoriness to insulin. The serious results of overdosage are as specific as those of desoxycorticosterone, and like them may appear after weeks of cumulation.

The response of the heart to digitalis is a most significant matter in assessing the nature of the disease process in each case. It proves that while coronary disease, hypertension, valvular lesion, hyperthyroidism, or some other condition may be contributing to the burdens borne by the ventricular muscle, an important factor is a metabolic defect, leading to delay in myocardial recovery from contraction. Because such a defect is more and more frequent with aging, old cardiacs respond more often to digitalis than do younger ones. The effects of digitalis on heart failure in a group of young people with rheumatic valve lesions and severe pulmonic hypertension are very much less striking than in old people with arterial hypertension and congestive failure.

If the heart failure of old people were due solely to inadequate blood flow in the myocardium, it is unlikely that digitalis would be of much use, for it is of no value in anginal disorders where myocardial ischemia obviously is the basic defect. The onset of failure usually ends a pre-existent angina, and digitalis therapy of failure may unmask concealed coronary disease by bringing out angina as the myocardial function improves. These phenomena find a parallel in the way in which fatigue of voluntary muscle defers or prevents the pain of the forearm muscles which are exercised after cutting off the arterial inflow.

The brilliant effects of digitalis on heart failure in older people made clinicians suspect that the disorder was not due simply to aging of the cardiac vascular supply, or to hypertrophy of muscle outgrowing the coronary bed. This has been fully confirmed by measuring the capacity of the coronary bed post mortem in cases of cardiac hypertrophy and failure. Heart failure must be a metabolic disorder of the myocardium in all cases in which digitalis produces a definitely favorable response, as it is inconceivable that it could alter fibrosis, anatomical defect, or ischemia of the heart. We have no more idea of what the defect is than we have of the defect in metabolic activity corrected by liver extract or by desoxycorticosterone, but the clinical significance of the response is equally decisive in each case.

The growth of our knowledge of digitalis is so steady and important that every physician who wishes to use these substances effectively and intelligently needs to review the subject every few years in a thorough and painstaking fashion. Dr. Movitt has done this for himself, and made his review available to assist his colleagues in this necessary task. For one reader this has been an entertaining and stimulating experience.

WILLIAM DOCK, M.D.

New York

DIGITALIS AND OTHER CARDIOTONIC DRUGS

Introduction

DIGITALIS, with its derivatives, holds an unchallenged position in the field of therapeutics. Although one of the older remedies known, it is still indispensable in the practice of medicine. Its importance is further emphasized by widespread usage. With the growing trend toward longer life expectancy, more people are reaching the age group where the degenerative type of heart disease is prevalent. This tendency still further enhances the usefulness of digitalis.

It is obvious that a thorough knowledge of this important therapeutic agent is essential to both the general practitioner and the specialist. Its therapeutic application is subject to a variety of modifying conditions. All the implications of such qualifying factors must be clearly understood for the judicious use of the drug. It has been said that a lifetime is not long enough to learn all about digitalis.

There has accumulated to date voluminous literature on the subject. In addition to innumerable articles, a number of monographs have been written. The most recent among them (1936), and an admirable work, is the monograph by Luten. However, more recently some of the concepts of digitalis therapy have undergone certain changes. With the introduction of new purified cardiac principles, the therapeutic possibilities have been enlarged. It is the purpose of this book to present recent advances in digitalis therapy along with a general discussion of the subject.

Developments in the field of discovery and application of the cardiac glycosides have represented the prevailing tendency in therapeutics toward purification of the medicinal agents and their reduction whenever possible to active and pure principles. Thus an attempt has been made to circumvent the uncertainty of the composition of galeni-

cal preparations by supplying products of constant composition, which are readily absorbed, rapidly effective, and well tolerated. Of the cardiac principles available, some have not attained widespread usage for various reasons, while others have achieved greater prominence. Among the latter, lanatoside C is rapidly gaining rather wide application and promises to become one of the most useful preparations in digitalis therapy. However, as in the words of Stoll, 'No matter how excellent a cardiac glycoside may be, the physician will always play an important and often a difficult role in view of the great variability in patients suffering from cardiac disease. He must depend upon his art to adapt himself, diagnostically and therapeutically, to every single case and its medicinal treatment.'

The discussion of cardiac glycosides may hardly be divorced from the consideration of their mother substance, the whole leaf digitalis. Therefore, in this presentation the description of the properties of the latter will precede that of all other products, and will thus serve as an introduction. The pharmacological properties and indications for use are in all essential aspects identical for the group as a whole. To avoid repetition the discussion of pharmacology and clinical applications in their broader aspects will be limited to the first chapter on digitalis and will be understood to apply to the entire group. Whatever differences may be found between the chemically pure glycosides and digitalis will be considered in the appropriate chapters.

CHAPTER I

Digitalis Folium

Historical Data

The first mention of the medicinal usage of foxglove by Welsh physicians in the thirteenth century antedates, by some three hundred years, the original botanical description of the plant. In 1542 Fuscius gave it the botanical name of ' Digitalis purpurea ' because of the resemblance of the flower to a finger, and its purple color. While some considered it a poison (Boerhaave), others early recognized its medicinal properties (Alston). However, for many years the specific therapeutic actions of the drug remained unknown and it was used as a panacea for a variety of totally unrelated conditions, such as epilepsy, ulcers, and wounds. The toxic effects of the drug were recognized long before the discovery of the therapeutic properties. Gerrade (1597) and Parkinson (1640) speak of it as an expectorant or emetic, while Haller mentions it as a purge. It was incorporated into the pharmacopœias of that period, but finally fell into disrepute.

Many years later William Withering became interested in a secret remedy employed by an old woman of Shropshire for treatment of dropsy, a condition which was refractory to any form of therapy known to medical authorities of that century. Various herbs were used by this woman in her formula, but Withering's perspicacity, along with his knowledge of botany, led him to the discovery that foxglove alone was responsible for the beneficial effects. At first, using it on his sick poor, he failed to note the expected response. However, after an English nobleman had been cured of dropsy by an ' empiric,' he decided to give the drug another trial and finally succeeded in achieving brilliant results. After ten years of experience with the drug he

published, in 1785, his remarkable treatise *An Account of the Foxglove and Some of its Medical Uses; with Practical Remarks on Dropsy and Other Diseases.*[1] Withering noted the potent diuretic action of digitalis and advised its application chiefly for that purpose. However, he did not fail to observe the cardiac action of the drug, recording in his writings that the pulse ' was retarded to an alarming degree without any preceding effect,' and mentioned that it might be useful in other diseases not associated with dropsy. He also warned against the dangers of overdigitalization, describing some of the signs and symptoms of digitalis intoxication. The cause-and-effect relationship of the cardiac and diuretic actions of foxglove was not clearly recognized.

Although Withering's work marks the beginning of specific digitalis therapy, the mode of action of this medicinal agent remained obscure for many years and its use was founded on purely empirical grounds. Moreover, the clear-cut indications for its administration, as formulated by Withering, were not heeded and it was employed in the treatment of various diseases, such as phthisis, in which the asserted beneficial effects were more a matter of fancy than fact. While Withering failed to appreciate the nature of the relationship of the cardiac and diuretic actions of the drug, John Ferriar[2] emphasized the clinical observation in regard to the heart action of the foxglove, stating the diuresis was not ' a constant and essential quality of the plant,' and that the power of slowing the pulse was ' its true characteristic.' He found that the drug would relieve palpitation. At the same time Kinglake (1801) showed that the force of the pulse was increased by the drug – the first clinical recognition of the increased stroke volume of a digitalized heart.

In spite of the classical work of William Withering and several later writings on the subject, digitalis did not attain prominence until comparatively recent years. The issue remained beclouded throughout a good part of the last century. As late as 1840 Pererra was advocating the use of foxglove for pulmonary hemorrhage, while such men of medicine as Austin Flint in this country, and Stokes and Walshe abroad, heeded but very little the teachings of Withering. The credit for the ' rediscovery ' of digitalis goes to Sir James Mackenzie, who awakened medical conscience to the recognition of the great potentialities of the drug and firmly established it as an indispensable therapeutic principle. Although this marks the beginning of the new and modern era of digitalis therapy, the use of the drug was at first limited to only one particular type of cardiac disorder. The broader aspects of

this form of therapy, as we now know it, eluded for a time full and well deserved recognition.

Mackenzie was impressed by the digitalis-induced slowing of the ventricles in auricular fibrillation. This observation, with the endorsement of Sir Thomas Lewis, led to the notion that the ventricular slowing in fibrillation of the auricles constituted the principal therapeutic effect of digitalis and that auricular fibrillation, therefore, was to be regarded as the chief, if not the sole, indication for treatment with this drug. Other possibilities were overlooked and attention remained focused on cardiac arrhythmias as the particular field of therapeutic exploits. It is regrettable that this notion, strangely enough, remains firmly entrenched in the minds of many practicing physicians who are entirely oblivious of the true mode of action of digitalis and indications for its use. Some still adhere to the belief that cardiac arrhythmia in itself, regardless of the cardiac status in all its entireness, calls for the administration of the drug. It is only within the last twenty-five to thirty years that knowledge of the enormous value of digitalis in the treatment of heart failure in general has gained ascendency. However, as early as 1910, Wenckebach emphasized the usefulness of the drug in the treatment of cardiac decompensation with regular rhythm.

Source and Chemical Structure

Although many species of the digitalis plant possess the same action varying in potency, Digitalis purpurea is the only species used as a source of the official preparation. The plant is a flowering biennial, found in many states of this country. Both the seed and the leaf contain the active principles. The drug is obtained from the leaf only.

Glycosides are the active constituents of digitalis. In their natural state glycosides are found in association with saponins, also glycosidic substances, which affect the solubility of the cardiac principles, but are inert therapeutically. The glycosides are formed by a combination of sugar (pentose and others) with aglucone. It is to the aglucone that the glycoside body owes its pharmacological activity. Although inactive in their pure form, the sugars when combined with aglucones increase both the potency and toxicity of the active principle. In addition, they are recognized as affecting certain physical properties of this chemical combination, such as water solubility and diffusion through semi-permeable membranes (cell penetrability). Also the persistence of the cardiac action is determined by them. The aglucones can be liberated from their linkage with sugars in the glycoside moiety by acid

or enzymatic hydrolysis. Chemically they are related to the bile acids and sterols. The empiric formula is $C_{23}H_{34}O_{(4-8)}$. A cyclopentenophenanthrene nucleus is the basic structure to which is attached a lactone ring. Digitalis purpurea yields the glycosides digitoxin, gitoxin, and gitalin. Stoll[3] demonstrated that these glycosides are encountered in their natural state as precursors, or ' natural glycosides.' They are deacetyllanatoside A and B in the leaves of Digitalis purpurea. Upon enzymatic hydrolysis deacetyllanatoside A and B yield the glycosides digitoxin and gitoxin respectively. While the sugar found in combination with the corresponding aglucone is the same (digitoxose) in the case of all three glycosides of Digitalis purpurea, the aglucones are different. Digitoxigenin, gitoxigenin, and gitaligenin are the aglucones of the glycosides digitoxin, gitoxin, and gitalin respectively. Digitoxin is pharmacologically the most important constituent of the three. A more detailed discussion of the chemical structure and properties of the various cardiac glycosides, found not only in Digitalis purpurea but also in other species of the plant and from other sources, will be found in the chapter on pure principles.

Pharmacology

The maintenance of circulation entails a complex interplay of a number of physiological factors. The heart rate, cardiac output as measured by stroke and minute volumes, peripheral resistance, and blood pressure are so closely interrelated that the alteration in any one of these variables usually affects, directly or reflexly, any one or all of the others. This makes the appraisal of the action of a therapeutic agent on each one of them separately a difficult matter. The clinical effects of the drug reflected in the sum total of the altered state of circulation are not always amenable to analysis of the component parts. However, in the course of careful, extended, and controlled studies, certain aspects of the pharmacological properties of digitalis have been elucidated and are now well understood, while others await further investigation.

Dock and Tainter[4] have demonstrated in their experiments on dogs that digitalis in therapeutic doses has a constricting effect on the smooth muscles in the hepatic vein. As a result of this particular action of the drug, the blood is pooled in the liver and the portal system. The storage of blood in the splanchnic area reduces the circulating blood volume, this leading to a fall in venous pressure. Katz and collaborators[5] claim to have demonstrated in their experiments on the isolated heart of the

DIGITALIS PURPUREA

dog that digitalis does not directly affect the myocardium under ' physiological ' or pathological conditions.

The results obtained by Dock and Tainter have been misinterpreted. Some workers understood these authors to imply that the peripheral effect of the drug as demonstrated in normal dogs was to be interpreted as the mode of action of digitalis in congestive failure. Thus Gold and Cattell[8] go to great length to show how the acceptance of this ' theory ' would entail the revision of the traditional concept of the causal relationship between venous stasis and heart failure. They point out that the increase in venous pressure is regarded as the result rather than the cause of heart failure, and that in ' isolated ' left ventricular failure digitalis restores compensation without notable changes in venous pressure. They also emphasize the fact that the ' theory ' implies that congestion in the liver should increase with digitalization due to the impediment of venous return caused by the digitalis-induced constriction of the hepatic vein. This would stand in flagrant contradiction to the clinical finding of shrinkage of the liver with the restoration of compensation under the influence of the drug. However, Dock and Tainter have never meant to translate their findings in the dog into terms of pharmacodynamic effects of digitalis in cardiac patients. They clearly indicate that the anatomical structures are not exactly analogous in the two species (canine and human). While in the dog the smooth muscles in the hepatic vein are abundant and may be conceived of being able on contraction to constrict the lumen of the vessel and thus impede the venous return, in the human the smooth muscle in the hepatic vein is sparse. They emphasize that in man the hepatic venous effect is slight, or nil, and that reduced cardiac output found in normal human subjects on administration of digitalis may be due to lowered muscular tone, or the pooling of the blood in the skin, lungs, and other organs. Dock and Tainter merely demonstrated that the decrease in cardiac output in the absence of failure is not due to the cardiac effect of the drug, but rather to its peripheral action. Cohn and Stewart and Harrison believed that it is due to direct effect on the heart. If this were true, venus pressure would be expected to rise with decreased output by the heart. What Dock and Tainter wished to indicate was that digitalis has no effect on the normal mammalian heart, while greatly affecting efficiency of the failing heart. In the normal animal, digitalis affects the vomiting center, the vasomotor and vasopressor systems, and cardiac irritability.

The view of Katz that the drug has no direct effect on the myo-

cardium is not shared by other investigators. Plant, Visscher, Cattell and Gold, and a number of Dutch and German investigators have demonstrated the marked direct effect of digitalis on the heart. This constitutes the most important pharmacodynamic action of the drug.

Action on the Myocardium

Pharmacological investigations at the turn of this century[7,8] have demonstrated a potent and direct action of the drug on amphibian and mammalian hearts. Plant was the first to demonstrate in heart-lung preparations the increase in cardiac efficiency under the influence of digitalis. The weight of the accumulated evidence of both experimental and clinical nature is in favor of the view of the direct effect of the drug on the human heart. However, in the camp of believers in the direct cardiac action there is no unanimity of opinion on the precise mechanism responsible for such an effect.

The original observations of Mackenzie[9] on the effect of digitalis in auricular fibrillation led to the general impression that slowing of the cardiac rate was the cardinal property of the drug. Straub first ascribed this action to the production of A-V block, and Cushny confirmed this view. It was thought that ventricular slowing was primarily responsible for the restoration of compensation and that fibrillation of the auricles constituted practically the only indication for the institution of this form of therapy. The possibility of primary action on the myocardium was ignored. However, in subsequent years, it has been clearly demonstrated by clinical studies of Pratt, Christian, Luten, and Marvin that digitalis could be of an equally great value in restoring compensation in cases of heart failure not accompanied by any disturbance of rhythm. The conviction that digitalis is chiefly effective in congestive heart failure regardless of the rhythm gradually grew and finally became a part of common knowledge. In this connection, the view that the direct action of the glycoside on the myocardium rather than the cardiac slowing *per se* is responsible for relief of congestive failure has gained prominence. The slowing of the heart rate is thus regarded by many as the effect rather than the cause of the recovered compensation.

The nature of the biochemical action of digitalis on the heart muscle is not clearly understood. It was originally maintained that there is a selective distribution of the absorbed or 'assimilated' glycosides in the different organs of the body, the cardiac tissue displaying particular avidity for the active principles, consequently storing more than its share of the drug. It has been since demonstrated that other tissues absorb digitalis substances as

readily, the heart muscle, however, being more susceptible to their effect.[10] Cloetta[11] advanced the theory that the glycosides are capable of diffusing through semi-permeable membranes and thus are able to penetrate through the cell envelope into the protoplasmic mass. There the glycoside molecule undergoes splitting into its cardio-active portion (aglucone) and the pharmacologically inert sugar. The aglucone may act by increasing the hydrophilic phase of the muscle fibers. By virtue of some chemical and physical processes, it is believed to increase the ability of the muscle fibers to swell, thus leading to stronger contractions and greater facility in relaxation. Still another explanation is that of Stroud[12] who asserted that the cardiac glycoside and cholesterin combine to form a cholesteride which is utilized in this form. Hermann and Decherd[13] thought that changes in the creatinine content of the heart muscle play an important role.

It has been found that lanatoside C administered to animals in 'therapeutic' doses may cause a slight increase in heart-muscle potassium, while 'toxic doses cause a marked decrease in the potassium content.'[14] It has been suggested that with toxic doses the intracellular potassium content is decreased apparently in exchange for sodium, since there is approximately an equivalent increase in intracellular sodium content.[15] In this connection it may be remembered that the potassium ion is known to be necessary for normal cardiac function.

Wollenberger[15a] has reported that the cardiac glycoside (ouabain) increases the oxygen uptake of slices of guinea pig heart muscle in the presence of glucose or lactate. This increase may be followed by depression. Among a variety of other guinea pig tissues studied, brain cortex alone responds in a similar manner. Whereas one may be tempted at first to regard stimulation of respiration by the drug the equivalent of its therapeutic action *in vivo*, the author has concluded that the increase in respiration and the subsequent depression are manifestations of those changes, presumably in the cell surface, that induce the myocardial fiber to contract with greater force.

Rothlin[15b] has studied the subject of the binding of glycosides by blood proteins. This problem has also been the subject of earlier studies by other investigators (Yernaux, Hoekstra, Lendle, and Bennhold). Rothlin has found that the glycoside-binding power is fundamentally the same, whether the serum is derived from the same species of animal or from a different one. The differences which exist are only quantitative, human serum and blood (heparinized) in particular exhibiting a stronger binding power than the serum of experimental animals. However, considerable differences exist among the various glycosides. For example, glycosides such as lanatoside A and digitoxin are very strongly bound, while lanatoside B, digitoxin, and scillaren A are only

fairly strongly bound; k-strophanthoside and lanatoside C are practically not bound at all by blood serum. Rothlin has found that the inhibition of the glycosides due to binding by blood proteins is not due to a destruction of the drug, but can be better explained by assuming that an inactive compound is formed between the glycoside and certain components of the blood. In other words, we are dealing here with an adsorption compound with proteins (albumin). The variations in the behavior of the glycosides with regard to their binding by serum albumin can be explained on structural chemical grounds. This author has felt that the protein-glycoside binding influences the rapidity with which the drug acts. The delayed onset of action of some glycosides can be explained by this adsorption phenomenon.

Attempts have been made to determine the differences in the distribution of the various cardio-active principles in the individual organs of the body. Rothlin[15b] has found that the heart muscle takes up, per unit of weight, 35 times as much glycoside, and the abdominal organs 4.5 times as much glycoside, as do the organs of the eviscerated animal minus the heart. These figures appear to give convincing proof of the selective fixation by the heart. To this must be added the fact that on no other organ or function can an action be demonstrated with so small doses of the drug as on the heart.

Whatever may be the biochemical mechanism of digitalis action on the myocardium, the fact remains that the drug enhances the force of systolic contraction of the diseased and dilated heart. This has been repeatedly demonstrated by a great many investigators directly on the isolated strips of muscle, in isolated amphibian and mammalian hearts, in heart-lung preparations, and in intact animals.

The work done by a muscle is related to its length. Within certain limits, with stretching more energy can be released. This general rule is known in its particular application to the heart muscle as Starling's law of the heart. With myocardial weakness due to damage from any cause, the ventricles are unable to expel properly the blood contained in their chambers and the heart dilates to accommodate the accumulated blood. The increase in diastolic size is accomplished through the stretching of the myocardial fibers. As a result, and in accordance with the law stated above, the amount of energy liberated in systolic contraction is increased, and so is the amount of work done. In other words, ' The ability of the heart to do larger amounts of work at greater diastolic volume results from the fact that the

amount of energy liberated in contraction is dependent upon the diastolic volume or fiber length.'[16] This leads to the important conclusion that dilatation of the heart in congestive failure represents a compensatory phenomenon. The diastolic size of the heart increases and the longer muscle fibers can respond with a more forceful contraction necessary to compensate for the inherent weakness. However, as failure increases, the limits of compensation may be exceeded and the various signs of circulatory failure then make their appearance. The dilatation of the heart in failure is a well established clinical finding. It has been demonstrated by Visscher[17,18] that this change in the behavior of the failing heart is due not to a decrease in total energy liberation, but to a decrease in the efficiency with which energy can be utilized; that is, the pathological heart dilates to compensate not for decrease in total energy liberated, but for decrease in efficiency with which the energy can be utilized. Thus the diseased and failing myocardium is a less efficient machine than it is in health. Under these circumstances digitalis exerts its beneficial effect on the failing heart by its ability to restore the organ's efficiency in doing work toward the normal.[19] Due to the improvement in efficiency of systolic contraction, the diastolic fiber length is shortened.

It must be conceded that there may be in addition other mechanisms operative in the restoration of cardiac function toward the normal. Fishberg[19] feels that digitalis also combats fatigue of the heart muscle. He states that heart failure is often ' the result of a change in the metabolic state of the heart muscle analogous to what is known as fatigue in skeletal muscle,' and that ' this altered metabolic state is characterized by decreased efficiency, i.e., by diminution in the proportion of liberated energy which is converted into mechanical work.' This is in agreement with the conclusions drawn by Visscher. But Fishberg goes on to say that '. . . A fundamental element in the salutary effect of the drug is slowing of the heart with resultant increase in the rest period of the heart.' Here Fishberg's view approaches that of Mackenzie and Lewis.

Thus there are several views in regard to digitalis action on the failing circulation and the ways in which it may be conducive to the alleviation of heart failure. They may be summarized as follows:

I. The reduction in the amount of work done by the heart (Harrison, Cohn, and Stewart).

II. The effect on the conducting system – A-V block (Straub, Cushny).

III. The increase in efficiency of systolic contraction (Plant, Bodo, Visscher, Gold and Cattell).

The improvement in circulation brought about by digitalis is reflected in an alteration of a number of physiological functions: the cardiac output and the velocity of circulation are increased, the venous congestion is relieved, and the venous pressure falls.

Cardiac Output

Reports on the action of cardiac glycosides upon the stroke output of the human heart in the presence of failure are contradictory. Cushny[7,8] found by using the myocardiograph that the increase in the force of systolic contractions compensates for the slowing of the rate with the net result of 20 to 30 per cent increase in the cardiac output. On the other hand, he also found that when excessive doses are administered the cardiac output falls, the increase in stroke volume apparently not being sufficient to compensate for the marked decrease in rate.

However, more recent studies have emphasized the complexity of the problem and have given rise to diversity of opinion. Cohn and Steele[20] have demonstrated the increase in minute output from the failing dilated hearts of dogs in heart-lung preparations. With it there was a decrease in the pressure in the right auricle and diminution in the diastolic volume of the heart. Using Grollman's original acetylene method, Stewart and Cohn[21] have confirmed the findings given above in their studies on patients in congestive heart failure with decreased cardiac output and cardiac dilatation. Digitalization of these patients, regardless of whether they had normal rhythm or auricular fibrillation, led in all to an increase in minute volume, diminution in heart size, and fall in venous pressure if it was elevated initially. On the other hand, Harrison and his associates[22] failed to secure consistent results with the Grollman method. McGuire, Hanenstein, and Shore[23] also found that the effect of digitalis upon the cardiac output was variable. La Due and Fahr[24] felt that neither the Grollman technique nor the direct Fick method can measure accurately the stroke output of the left ventricle if aortic or mitral insufficiency is present. ' It is possible that some mitral regurgitation may occur in many cases of heart failure associated with dilatation of the left ventricle and the methods just mentioned will not measure ventricular output accurately in such instances.' In their roentgenkymographic studies on patients with heart failure and normal sinus rhythm they found with digitalization an in-

crease in the stroke volume and a decrease in the diastolic size of the heart. From all these observations it would appear that on administration of digitalis to patients with subnormal cardiac output due to heart failure, the cardiac output generally increases, but that this is not invariably the case.

Intravenous catheterization of the heart has opened new and hitherto unrealized approaches to research. One of its great values lies in permitting determination of cardiac output according to the Fick principle. By using this new technique McMichael and Sharpey-Schafer[24a] have recently made a new contribution toward a solution of the problem of the effect of cardio-active principles on cardiac output in heart failure. These authors again emphasize the peripheral effect of the drug. Their theory serves as an extension of the earlier work by Dock and Tainter (1930), who demonstrated that digitalis lowered the venous pressure in dogs, an observation since confirmed in normal man by Rytand (1933). It also harmonizes with the view of Katz (1938), who, on finding a fall of venous pressure resulting from digitalis in the whole animal, suggested the possibility that the action of digitalis bodies in congestive heart failure might be due solely to this peripheral action.

On injecting digoxin (the glycoside of Digitalis lanata) intravenously in a single dose and measuring the effect on right auricular pressure and cardiac output, McMichael and Sharpey-Schafer[140] have demonstrated in patients with congestive failure a fall in the auricular pressure, while the cardiac output, initially low, rose toward normal in spite of the fall in venous pressure (see Fig. 1). A similar effect was noted in patients with heart failure on lowering of right auricular ' filling ' pressure by simple mechanical measures, such as the application of cuffs about the extremities. In these instances also the cardiac output increased as the venous pressure fell. On the basis of these findings the authors concluded that the effect of the drug might be accounted for by the primary action of the glycoside on the venous pressure. They found support for their theory in the Starling curve of cardiac output of an overloaded heart (see Fig. 2). As the venous pressure is increased a stage is reached at which the curve of cardiac output response at first flattens and then begins to drop. McMichael and Sharpey-Schafer argued that in cardiac failure often accompanied by high venous pressure the overloaded heart is ' over the top ' of the curve. Increase in filling pressure in the case of a failing heart is accompanied by an increase in the output until a certain critical point when the heart be-

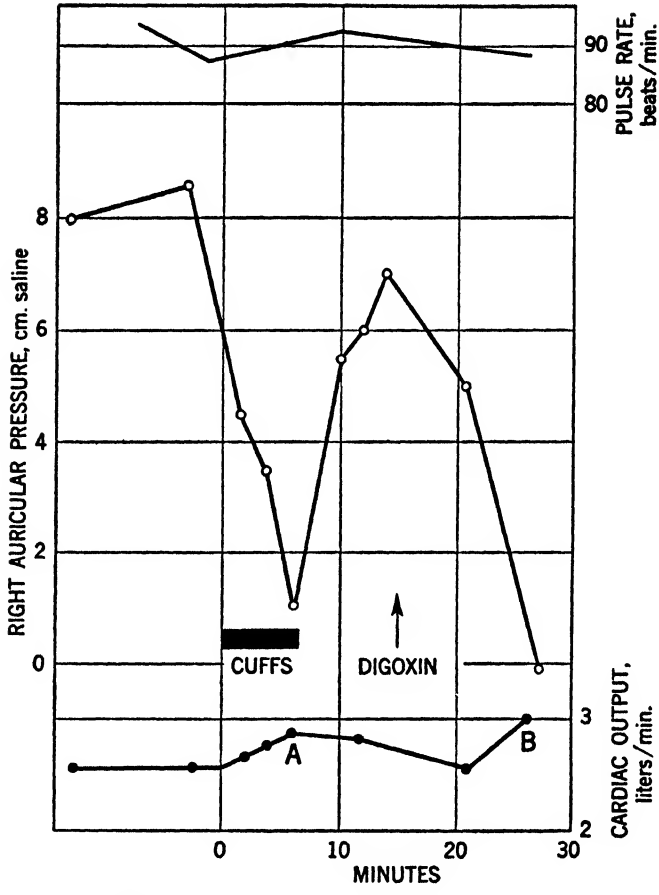


FIG. 1. Hypertensive failure with sinus rhythm. A. Lowering of right auricular pressure by means of congesting cuffs on the thighs produces a small but significant increase in cardiac output. B. After release of cuffs, 1.5 mg. digoxin produces a similar increase in cardiac output. (From J. McMichael, 'Circulatory Failure Studied by Means of Venous Catheterization,' *Advances in Internal Medicine*, vol. II, 1947, Interscience Publishers, Inc.)

comes overloaded; thereafter the output begins to fall with any further increase in pressure. However, the data of these authors also indicate a significant rise in cardiac output in patients with congestive failure even in the lower ranges of venous pressure. This evidence points to some other primary factor, such as increased myocardial efficiency, operative in inducing improvement in cardiac output.* It should also be pointed out that these investigators have measured only central

* At a recent meeting of the American College of Physicians (1948) McMichael conceded that ouabain, in contrast to 'digoxin, may have effect on the myocardium.

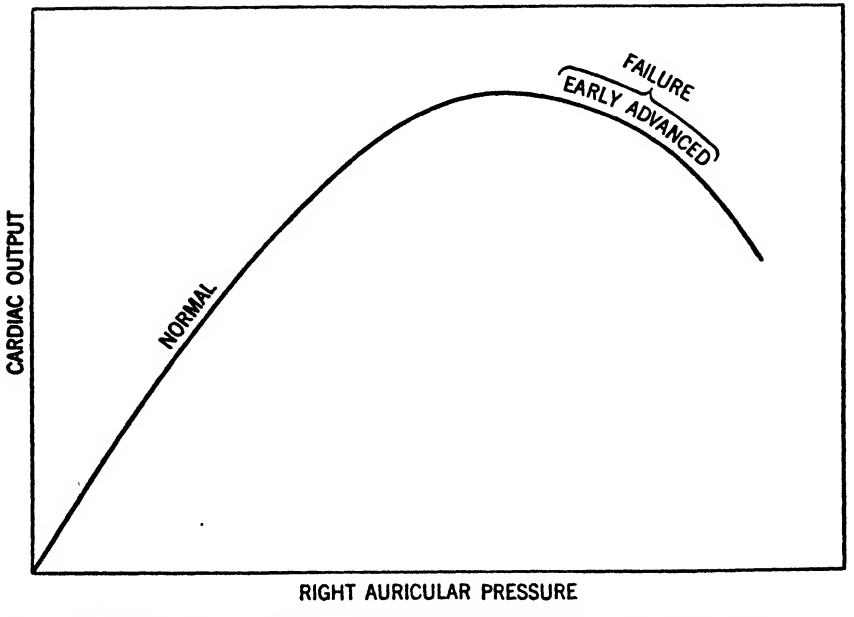


FIG. 2. Starling's curve. Increase of filling pressure is accompanied by increase in cardiac output until the heart is loaded; thereafter output begins to fall. (From J. McMichael, 'Circulatory Failure Studied by Means of Venous Catheterization,' *Advances in Internal Medicine*, vol. II, 1947, Interscience Publishers, Inc.)

(auricular) pressures while implying peripheral venous pressure changes. Hemodynamically the two may not be synonymous.

The observations of McMichael and Sharpey-Schafer on lowering of right auricular pressure by the application of cuffs about the extremities in patients with heart failure, leading to increase in the cardiac output, are similar to the results obtained by venesection. Venesection in patients with congestive failure leads to a fall of venous pressure which may be accompanied by a rise in cardiac output. Stead[24b] states that recent observations by Hickam and Cargill[24c] on the effect of exercise on the cardiac output of patients with congestive failure are helpful in the interpretation of these findings. These investigators have found a fall below the resting level in the cardiac output during exercise in patients with severe congestive failure. The heart in these patients, already inadequate even at rest, when pushed harder becomes still less adequate. With the cessation of effort the cardiac output presumably returns eventually to the resting level. These observations seem to indicate that in the presence of heart failure any procedure which normally decreases the work of the heart may result

in an actual increase in the output. Lowering the venous pressure by venesection tends to reduce pulmonary congestion, diminish reflex activity, and in certain instances lower the arterial pressure. These effects may reduce the body requirements for blood. In severe failure of the circulation decreasing the load on the heart by venesection may thus cause a rise, rather than a fall, in cardiac output. Whereas the application of cuffs about the extremities leads to a decrease in venous pressure and thereby an increase in cardiac output, as found by McMichael and Sharpey-Schafer, the question arises as to whether or not the effect of the drug on cardiac output in patients with congestive failure results from the operation of similar mechanisms. In contrast to orthodox concepts, these English authors draw attention away from the stimulating effect of cardio-active principles on the myocardium itself. While their findings may be applicable to digoxin which they have studied, it does not necessarily follow that the same findings hold for the entire digitalis group of drugs. They also suggest that digoxin may accordingly be actually harmful when administered to patients in whom high cardiac output exists in heart failure, as, for example, in cor pulmonale, anemia, and Paget's disease (in the latter disease the circulatory dynamics are somewhat similar to the condition existing in the presence of arteriovenous fistula). The author has not found digitalis to be particularly helpful in patients with cor pulmonale, but at the same time has failed to note any deleterious effects from digitalization of such patients.

The results of other investigators employing the heart catheterization method are at variance with those reported by McMichael and Sharpey-Schafer. Stead *et al.*[24b] have reported the data on changes in circulation produced by the intravenous administration of 1.6 mg. of lanatoside C in twenty-two patients with congestive heart failure. The data are quite consistent and demonstrate that in patients with congestive failure the drug produces a rise in cardiac output, an increase in stroke volume, a rise in systolic and mean arterial pressures, and a fall in atrial pressure and in peripheral resistance. The increase in cardiac output occurred in patients with normal rhythm, paroxysmal auricular tachycardia, and auricular fibrillation. The increase in cardiac output was accompanied by a rise in mean and systolic arterial pressures. The authors felt that this rise was not so great as it would have been if the peripheral vessels had not dilated. Apparently the fall in peripheral resistance was not sufficient to offset completely the effect on arterial pressure of a rise in cardiac output. The data show no

relation between the magnitude of the fall of venous pressure and the degree of increase in cardiac output, although the first measurable effect of the drug was on the atrial pressure (The average fall during the first 60–120 minutes was 62 mm. of water.). The authors have concluded that the results of the investigation support the thesis that digitalis has a direct effect on the strength of the contraction of the ventricles and that its effect is not dependent on a reduction in cardiac rate.

Bloomfield *et al.*[24d] have obtained results somewhat similar to those of Stead and his collaborators in their studies on the effects of ouabain upon the dynamics of the circulation in congestive heart failure. The drug was administered by the intracardiac route; the glycoside was injected through the catheter over a period of 1–2 minutes in doses of 0.25 to 0.75 mg. Thus the right side of the heart was catheterized not only in order to obtain samples of mixed venous blood and to measure the right atrial pressure but also for the purpose of administering the cardio-active principle. Effects on the circulation were noted within 1–8 minutes and were characterized by an increase in the systemic systolic and pulse pressures and in the right ventricular systolic and pulse pressures. When measured, increases in the pulmonary arterial systolic and pulse pressures were also observed. While ultimately there was evidence of diminished venous pressure in the right ventricle, measurement of the peripheral venous, auricular, or ventricular diastolic pressure shows these values to be essentially unchanged at the time the other pressure rises. There was consistently an increase in cardiac output attributable to an increase in stroke volume. The latter was found usually to precede cardiac slowing or any decrease in peripheral venous or right ventricular filling pressure. The latter effects usually did take place, but later. The authors have justifiably concluded that the increased stroke volume and cardiac output can best be explained as a direct action of the drug upon the failing heart, this action presumably exerting its influence upon the contractility of the myocardium.

Werkö and Lagerlöf[24e] have obtained similar results in their investigations of the effect of lanatoside C on the circulation in patients with congestive failure. The same method of catheterization of the heart was employed for measuring the right atrial pressure and obtaining samples of mixed venous blood. The dose of the glycoside was 0.8 mg. It is an interesting fact that in patients with cardiac decompensation the auricular pressure decreased in most but not all instances, while

the minute volume always increased. There were only insignificant changes in the pressure in the lesser circulation. In cardiac patients with good compensation the minute volume remained unchanged or changed only slightly.

It is important to realize that the influence of digitalis in health is different from that in disease. Several observations were made showing that in normal hearts the drug may cause diminution in heart size and cardiac output. Cohn and Stewart[25] noted decrease in minute volume and heart size in normal dogs to whom digitalis was administered intravenously. They interpreted their findings as follows: The cardiac output is the net result of two opposing factors under the influence of digitalis. The first of these effects increases cardiac ' tone ' and results in decrease in the size of the heart, tending to diminish the cardiac output. The second effect increases ventricular contraction and tends to increase the cardiac output. In case of a normal heart the ' cardiotonic ' action of the drug leads to decrease of the heart below its optimal size, which more than counterbalances the effect on the force of systolic contraction; because of smaller size there is a smaller than normal amount of blood in the ventricular chambers to be ejected during systole. While there is a difference of opinion whether or not the myocardium can be demonstrated to exhibit the properties of ' diastolic tone,' and many investigators may thus not agree with the interpretation by Cohn and Stewart regarding the mode of action of digitalis on the myocardium, the fact remains that the findings above on cardiac output in health have been confirmed by other workers, both in experimental animals[26] and in normal human beings.[27] All these effects have been shown by Dock and Tainter to be secondary to diminished venous return resulting from the peripheral action of the drug. Dock has expressed the belief that the diminution in venous return in human subjects may be offset by over-breathing. To the criticism of interpretations by Cohn and Stewart it can be added that these authors actually have not demonstrated any changes in diastolic tone, as they failed to measure the resistance to diastolic filling.

An explanation of this seemingly ' paradoxical ' effect of digitalis on normal circulation can be found in the work of Dock and Tainter[4] already mentioned. It will be recalled that they succeeded in showing diminution in venous return to the heart and in circulating blood volume caused by digitalis-induced constriction of the hepatic veins in a dog. Of course it remains to be demonstrated whether or not this throttle mechanism is also operative in man.

The ' paradoxical ' action of digitalis on cardiac output in health, as contrasted with its effect in disease, is explained by Fishberg[19] in the following manner. The drug affects cardiac output through two mechanisms: (1) By increasing the functional capacity of the heart which tends to augment cardiac output; (2) By decreasing the circulating blood volume and venous return, which tends to diminish cardiac output. In health the venous return is the determining factor, for a normal heart is able to propel any volume of blood delivered to it under physiological conditions. The increase in the functional capacity of the heart under the influence of digitalis does not come into play. At the same time the action of the drug on the peripheral vessels (Dock and Tainter) resulting in diminution of venous return leads to decrease in cardiac output. On the other hand, in case of a failing myocardium both the venous return and the functional capacity of the heart determine the cardiac output. As the latter is subnormal in congestive failure, the increase in the cardiac efficiency due to digitalis may well be expected to result in increased output. The lack of this particular finding of increased cardiac output in some patients may be explained by the fact that in them the peripheral effect of digitalis, leading to decrease in circulating blood volume and venous return, is predominant.

The changes in heart size and stroke volume in cases with compensated organic heart disease (without congestive failure) are variable and entirely unpredictable. Stewart *et al.*[28] found that while some patients showed changes similar to those observed in congestive failure, in others there was diminution in cardiac output comparable to the conditions prevailing in health; still others showed no change at all.

Venous Pressure

Increase in cardiac output results in lowering of venous pressure, if initially elevated.[19] This action apparently is secondary to the primary cardiac effect of digitalis. With augmented efficiency of the heart as a pump, the blood is propelled more effectively, the heart chambers are emptied more completely, and the venous stasis is relieved. In patients with normal hearts, or in those with left ventricular failure not accompanied by increase in venous pressure, digitalis is said to have no such effect. However, Rytand[29] has demonstrated a fall in venous pressure on administration of the drug to normal subjects.

At the same time the circulatory volume, usually increased in failure, is decreased with restoration of compensation.[30] The way this change is brought about by digitalis is not well understood.

With relief of failure, the velocity of circulation is increased. Circulatory velocity is largely conditioned by flow of blood through the venous system and is an index of dilatation of the veins and auricular chambers. With decrease in heart size the circulation time falls.

Cardiac Rate

The heart rate is affected by digitalis both in health and disease. In cardiac patients the rate may be affected not only in the presence of an arrhythmia, but also when the rhythm is normal. Mackenzie particularly emphasized this change in relation to ventricular slowing in auricular fibrillation. In fibrillation of the auricles the ventricular slowing by digitalis was so striking that originally all the beneficial results of digitalis therapy in congestive failure were attributed solely to this particular effect of the drug. Mackenzie was so impressed by the spectacular decrease in heart rate that he came to the conclusion that slowing alone was responsible for relief of failure and improvement in general condition. He also regarded the presence of arrhythmia as an important factor in the favorable outcome of digitalis therapy. The authenticity of this opinion, supported by Lewis, prevailed for some time and patients without auricular fibrillation were not thought to be benefited by the drug. However, Mackenzie himself has noted good results in two patients with regular rhythm.

The importance of other factors instrumental in bringing about improvement in the state of circulation has been disclosed in the course of clinical research of the last twenty-five to thirty years. In the light of present knowledge these factors have been recognized as playing a significant role in the slowing of the heart. In fact, the question has been posed by some whether or not cardiac slowing may in itself be dependent on these other factors and thus represent a secondary rather than a primary effect of digitalis action.

Cushny and Mackenzie held the view that digitalis-induced ventricular slowing in auricular fibrillation was brought about by the influence of the drug on the conduction system, causing a partial A-V block. With emphasis on A-V block, other possibilities were entirely overlooked. The direct action of the cardiac drug on the myocardium was not recognized and the possible consequences of such action were, therefore, ignored. Also the important role played by the Bainbridge reflex should not be forgotten.

Failure, like exercise, excites the Bainbridge reflex, which lowers the vagal tone, increases the frequency of impulse discharges from

the sinus node, and removes the inhibitory influence on auriculoventricular conduction. As a result, the cardiac rate is increased, as it would be for example on administration of atropine, which blocks vagal influence. Thus the tachycardia of auricular fibrillation in patients with cardiac decompensation may be the result of the failure itself rather than the cause of it. Digitalis reverses the changes brought about by this reflex.

The direct effect of digitalis on the myocardium has already been mentioned. It consists in enhancing the force of muscular contraction. With improvement in the state of circulation through increase in cardiac efficiency, the coronary flow is also improved, and the partial anoxemia of the heart muscle is thereby relieved. According to some investigators, this results in a decrease of myocardial excitability and consequently the threshold for activation of the ventricles by the auricular impulses is raised appreciably. It is further argued that the action of the drug on the junctional tissue, resulting in a partial A-V block and interfering with the transmission of the auricular impulses to the ventricles, is not then necessarily the only mechanism by which the ventricular slowing is brought about. Luten thinks that the action on conduction may not be so important as the other effect above described.[31] This explanation receives some support from the clinical observations on the ineffectiveness of digitalis in some cases of auricular fibrillation not associated with heart failure. Under these circumstances the drug may fail to cause ventricular slowing. In the light of this discussion, the reason for this therapeutic failure is made more obvious. The absence of congestive failure excludes the possibility of the beneficial effect of digitalis on the myocardium. The flaw in this theory lies in the fact that the increase of myocardial irritability by anoxia has not been actually demonstrated.

In cases of heart failure with regular but rapid rhythm, digitalis is also instrumental in slowing the cardiac rate. It is believed that the sinus tachycardia of a failing heart represents a compensatory phenomenon. Reference has been made to it as 'Nature's only method of maintaining an effective circulation.'[32] However, this would be a very expensive way. One has only to recall many patients with complete auriculoventricular dissociation in whom the circulation is adequately maintained, not infrequently in spite of an exceedingly slow ventricular rate. However, if the ventricle can effect only a small stroke volume, increased rate may increase cardiac output. It also has been remarked that in patients with little other evidence of myocardial

insufficiency the tachycardia may be the only evidence of 'occult' failure.[33] The Bainbridge reflex adequately explains the rapid beating of a failing heart. With diminution of the stroke volume in cardiac decompensation resulting in increase in venous and intra-auricular pressure, this reflex mechanism is called into play leading to the acceleration of the heart rate. On recovery of compensation under the influence of digitalis and the consequent fall of venous pressure this reflex mechanism ceases to operate and slowing ensues. The latter ' is rather a subsequent re-adjustment to improved conditions of the circulation, which would take place after improvement from any cause.'[34]

Effect on the Sinus Node

By some investigators the ventricular slowing in patients with regular rhythm is attributed to the influence of the drug on the auricular pacemaker via vagus nerve.[35] The heart rate normally is determined by the frequency of discharge of impulses from the pacemaker in the sinus area. Variations in vagal tone influencing the sinus node and thus effecting change in rhythmicity of the node are, of course, well known. Vagus stimulation slows the heart, while its inhibition causes acceleration. In animals digitalis has been shown conclusively to decrease the cardiac rate. That the action is mediated, at least to a large extent, through the vagus nerve is demonstrated by the fact that this effect can be abolished to a considerable degree by atropinization or vagotomy. It was formerly believed that the drug stimulated the vagal nuclei in the medulla. Other investigations tended to indicate that the drug might sensitize the pacemaker in the heart to normal impulses reaching it from the brain via the vagus. In cross-circulation experiments in animals it was shown that no slowing of the cardiac rate resulted from carotid sinus. The conclusion drawn was that the vaso-receptors in the carotid body were stimulated by digitalis to cause reflexly vagal perfusion of the vagal centers with the drug, and that the slowing depended upon the accessibility of the glycoside to the region of the slowing of the heart rate.[36] This observation finds some support in certain clinical investigations showing that in individuals with hyperactive carotid sinus reflexes digitalis may increase the excitability of the carotid sinus, enhancing the tendency to arrhythmias and cardiac arrest.[37] Perhaps regardless of any special sensitivity of this organ, slight slowing of sinus rate has been noted in normal individuals with exhibition of full therapeutic doses of digitalis. However, such slowing is far from being spectacular, usually ranging from 4 to 10 or 12 beats

per minute.[27,21] In patients with heart failure it may be that with the administration of digitalis the direct vagus influence on the pacemaker is sufficient to exert some effect and thus play a contributing role in the mechanism of cardiac slowing. To determine the exact extent of any such direct influence in clinical practice would be very difficult. It is possible that marked slowing in man by direct vagal effect is a toxic rather than a therapeutic manifestation of digitalis action.

Effect on the Conduction System

That digitalis has an influence on junctional tissue has been established beyond any doubt. Opinion is divided in regard to the manner in which the A-V block is produced by the drug. Although the conducting fibers of the bundle of His constitute a specialized type of myocardial tissue, they share with the latter the ' cardiotonic ' effect of digitalis. This effect fundamentally consists in strengthening the muscular contraction with the concomitant increase in refractory period and the corresponding decrease in the rate of conduction.[38] Thus the block may be produced by the drug through direct action on the conducting tissue. However, there are some who believe the block to be of vagal origin entirely. Porter[39] contends that failure to demonstrate the vagal effect by other workers was due to the employment of inadequate doses of atropine used in attempts to paralyze the vagus endings and thus effect the ' vagal release.' By administering large doses of atropine intravenously (1/25 grain) to patients with auricular fibrillation in whom ventricular slowing had taken place under the influence of digitalis, he succeeded in reproducing promptly the rapid ventricular rate of the predigitalization period, thus demonstrating to his satisfaction that the original slowing of the ventricles was caused by the action of the drug on the conducting system via the vagus. On the other hand, Gold and his associates[40] have noted that the slowing produced by small doses of digitalis was apparently due to vagal stimulation, with adequate doses of atropine increasing the heart rate, whereas after full doses of digitalis, atropine was found to be no longer effective in increasing the ventricular rate, the slowing apparently being due to extra-vagal action of the drug.

Movitt[41] has presented some evidence showing that the accessory conducting system (the bundle of Kent) may not share with the junctional tissue the cardiotonic effects of digitalis, with the result that digitalization does not appear to interfere with the passage of the sinus impulse to the ventricles via this aberrant pathway.

In summary, it may be said in regard to the possible mechanism of digitalis-induced relief of congestive failure, that the various factors emphasized by the proponents of different theories are not necessarily contradictory or mutually exclusive. On the contrary, they may in many instances supplement each other, as can be seen from the pre-

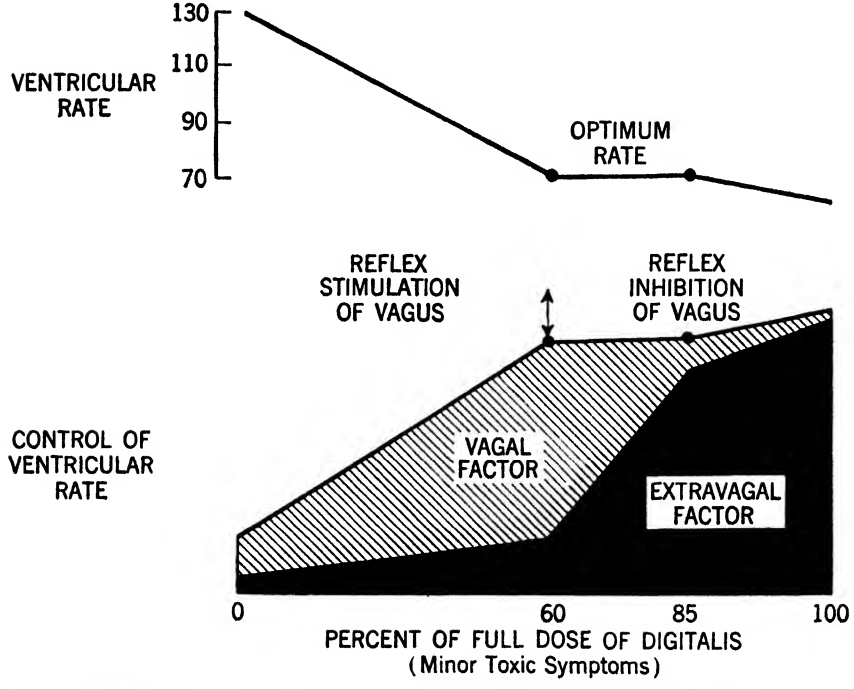


FIG. 3. Schematic representation of the mechanism by which digitalis slows the ventricular rate in heart failure with auricular fibrillation. (From H. Gold., *J. A. M. A.*, vol. 132, 1946.)

ceding discussion. The effects of the glycoside on the force of myocardial contraction and on the conducting system are probably the most significant ones.

Effect on the Blood Pressure

Both in health and disease the level of blood pressure is dependent on a number of interrelated factors and at any one time represents the sum total of direct and reflex adjustments between the various functions of circulatory dynamics, such as cardiac rate, cardiac output, and peripheral resistance. As the cardiac output is increased in heart failure under treatment with digitalis, this drug may well be expected to cause

some rise in the systolic level of blood pressure. However, as the mechanism of compensatory adjustment is brought into play, it can offset the initial tendency to rise. In fact, such variable results are observed in patients during the course of digitalis therapy. Slight-to-moderate rise in systolic pressure may take place, not infrequently accompanied by a slight fall in diastolic level. As a result the pulse pressure may increase.[21,42,48] There is no uniform effect on blood pressure. Frequently there is a temporary, but only moderate, rise in the systolic level. The results of therapeutic doses of digitalis upon blood pressure in patients with heart failure is thus quite variable. If there is a tendency for the systolic pressure to rise, this may be more than compensated for by reflex adjustments. The rise is usually non-significant and does not reach a level higher than that which is customary for the patient under normal circumstances.[34] From this it clearly follows that hypertension does not constitute a contraindication to the administration of the drug.

In patients without failure there is no notable effect on the blood pressure. In normal people the rise in systolic pressure is insignificant, if at all present, and when present is very transient.[21] As the cardiac output in normal people is not increased by digitalis (and even may be actually decreased), this slight rise in blood pressure when present can be explained by some degree of peripheral vasoconstriction. However, only when administered in toxic doses to animals has digitalis been found to exert a definite vasoconstricting effect leading to a rather appreciable rise in systolic blood pressure.

Effect on Peripheral Blood Flow

Clinicians are usually under the impression that the skin of patients with congestive heart failure, especially the skin of the extremities, appears to be cooler than normal. Objective measurements have been made relating to the temperature of the skin of certain areas of the body and to the rectal temperature in patients with heart failure, in an attempt to arrive at an understanding of the fever that occurs in heart failure unrelated to any infection. Some investigators have found that the temperature of the surface in patients with heart disease is lower than in normal individuals, while that of patients with infectious fever is as high as or higher than normal. As a result of these studies it has been concluded that the elevation of the rectal temperature in heart failure depends on processes incidental to heart failure itself.[48a] Certain experimental data of other workers have pointed out a decrease in the amount of peripheral blood flow in cardiac decompen-

sation, while others demonstrated a normal blood flow in the extremities. Stewart *et al.*[43b] have attempted to settle the controversy by carrying out objective measurements with respect to the total peripheral blood flow. The peripheral blood flow has been measured by them in patients with congestive heart failure before and after the administration of strophanthin K and digitoxin (digitaline Nativelle) intravenously (a modification of the Hardy-Soderstrom method was used). The authors have concluded that the amount of blood flow allotted to the whole periphery of the body is in the normal range during heart failure as compared with the amount in normal subjects at the same environmental temperature. Apparently in spite of the fact that the cardiac output is decreased in heart failure, there does not seem to be any restriction in the amount of blood allotted to the peripheral circulation. The average weighted skin temperature was found to be slightly increased in heart failure, with the temperature of the skin of the forehead being slightly cooler and of the feet slightly warmer than normal. There was also observed at the same time a rise in rectal temperature. The authors felt that although there was no alteration in the amount of blood flow through peripheral vessels in heart failure as compared with normal subjects, it was insufficient, because of its slow velocity in a dilated vasculature, to maintain an adequate elimination of heat in the face of the metabolic demands. Such circumstances would lead one to expect a rise in the internal temperature of the body. After the administration of the cardio-active principles mentioned above, the peripheral blood flow was observed to increase with the concomitant rise of the temperature of the skin. As a result, the internal temperature (rectal) fell slightly but usually failed to reach normal levels. The effects described above were found to take place more rapidly in the case of ouabain than with digitoxin.

Effect on Coronary Circulation

There is no unanimity of opinion on the effect of digitalis on the coronary arteries. Loeb,[44] who perfused the excised heart of a cat with a solution of digitoxin, found some reduction in the coronary flow. Voegtlin and Macht[45] also arrived at the conclusion that digitoxin is ' the most powerful coronary vasoconstricting constituent of digitalis leaf.' On the other hand, Bond[46] reported that digitalis had no effect on the velocity of coronary flow in the intact cat. Bodo,[47] using smaller amounts of the drug, obtained an increase in the flow. It has been pointed out that any undesirable coronary constrictor action which

might occur would be, to some extent, counterbalanced by an increase in cardiac efficiency and the resultant general improvement in blood flow. However, according to Anrep[48] the increased myocardial contraction actually interferes with the coronary flow. Gilbert and Fenn[49] made an extensive study of the effect of digitalis on the coronary flow of intact dogs and concluded that the drug may have a vasoconstrictor action on the coronary arteries. Finally, in the more recent studies on heart lung-preparations and intact animals, Ginsberg, Stoland, and Siler[50] demonstrated an early decrease followed by an increase in coronary flow after the administration of digitalis. The late effect, i.e. the increased flow, almost always followed the early reduction. They felt that any detrimental effects of the decrease which occurred during the ten-minute period immediately following the injection of the drug might be compensated for by the beneficial effects of the increase during the next period. It was concluded that the increased coronary blood flow of this second and longer lasting period was probably the result of the improvement in the general circulation which was caused by digitalis. These investigators thought that the contradictory nature of the earlier reports on the subject could be accounted for by the determinations of the coronary flow being made during the different periods following the administration of digitalis.

Adherents to the belief of coronary vasoconstriction cite in support of their view the clinical evidence of induction by digitalis of attacks of angina pectoris in susceptible patients.[49] On the other hand, more recently Gold *et al.*[51] in an extensive study of patients with angina pectoris without decompensation, demonstrated that administration of the drug did not have any influence on the incidence of coronary attacks. It should be remembered that heart failure inhibits angina much the same as fatigue inhibits pain in the ischemic voluntary muscle. Thus Gold and collaborators had the right approach to the study of this problem by selecting patients free from failure.

Diuretic Effect

In the early days of digitalis therapy the diuretic effect of the drug was well recognized, and in fact the presence of edema constituted the only indication for its administration. Withering adopted the use of foxglove for that particular purpose and, although he knew of other effects of digitalis on the circulation, he was not aware of the relationship between impaired heart action and edema on the one hand, and improvement in cardiac efficiency and diuresis on the other hand.

More than a century later Mackenzie, on noting the diuretic action of digitalis, still considered it as a manifestation of an extra-cardiac effect. It will be recalled that his attention was particularly directed to the spectacular slowing of the ventricles by the drug in cases of auricular fibrillation and that he regarded such slowing as the most important, if not the sole, mode of action of the active principle on the heart. In heart failure with normal rhythm, where cardiac slowing in the course of treatment is less spectacular, the occurrence of diuresis was then very naturally explained as due to extra-cardiac action of the drug. When more recently the direct effect of digitalis on the myocardium became recognized, it was no longer necessary to look for explanation outside of the realm of cardiovascular dynamics. The principal cause for accumulation of fluid in the interstitial spaces and in the serous cavities in congestive failure is directly attributable to the increase in hydrostatic pressure in the venous ends of the capillary system caused by venous congestion. With improvement in circulation the venous congestion is relieved. As a result, the hydrostatic pressure in the venous ends of the capillaries is decreased, thus allowing the resorption of the edema fluid back into the circulation. Another factor operative in the mechanism of diuresis is that the hypoproteinemia, incidental to poor absorption of nutrient material from the congested digestive tract and deficient intake because of lack of appetite, is corrected on recovery of compensation. This hypoproteinemia, by disturbing the normal osmotic pressure equilibrium, can be regarded as partly responsible for the edema in cardiac patients. At the same time the renal function is also improved by relief of vascular congestion in the kidneys, and the excess fluid absorbed back into the circulation from the edema depots may now easily find its way through the cleared glomerular tufts into the excretory units of the kidneys. Thus diuresis is directly attributable to improvement of renal circulation and not to direct stimulation of the kidneys.[52] Digitalis produces primarily a marked increase in glomerular filtration as a result of augmented circulation in the glomerular tuft and tubular capillaries.[53]

In normal persons or in patients with heart disease but without failure digitalis does not exert any diuretic effect.[54,55] In edema or anasarca of non-cardiac origin (nephritis, starvation edema, portal obstruction in hepatic cirrhosis) digitalis again is without any effect.[42] On the other hand, in nephritis complicated by heart failure, administration of digitalis may be followed by some diuresis.

In cardiac decompensation, digitalis alone, without any adjunct

therapy, may suffice to produce satisfactory diuresis and disappearance of all edema. However, many cardiac patients require additional and specific measures to promote diuresis. According to Marvin, less than 50 per cent of patients in heart failure with regular rhythm show a definite response to digitalis. His observations have been confirmed by many men having extensive clinical experience. Therefore, the employment of mercurial diuretics often becomes imperative. To neglect their use is to invite disappointment.

Effect on the Electrocardiogram

It is well known that digitalis causes certain changes in the electrocardiogram, some of which, although not really pathognomonic of the drug, are nevertheless rather characteristic. As these alterations from the normal in the tracing are not infrequently superimposed on the changes resulting from the underlying heart disease, the interpretation under such circumstances is not always a simple matter. This summation of effect should always be kept in mind in interpreting the electrocardiogram of a cardiac patient treated with the drug. It is important to learn how digitalis may modify other known patterns. Only thus can erroneous conclusions be avoided. The changes produced by digitalis may enable one to determine whether or not the patient has been receiving the drug in the last two or three weeks. In other words, they may serve, but in a limited sense, as an index of digitalization. However, one should bear in mind the fact that they cannot in themselves be regarded as an index of quantitative estimation of digitalis dosage or adequacy of digitalization. Also in some instances these changes may at times serve as confirmatory evidence of a clinical impression of digitalis intoxication.

Electrocardiographic abnormalities produced by the drug may simulate practically every known pattern produced by disease (with the possible exception of intraventricular conduction defects). There are seven distinct manifestations of digitalis effect with changes in: (1) P waves; (2) QT intervals; (3) Auriculoventricular conduction; (4) RS-T segments; (5) T waves; also the appearance of (6) Premature contractions; and (7) Other types of abnormal rhythm.

The least important are the changes in the P waves, consisting of lessened voltage and notching or the diphasic character of this particular deflection.[55]

The QT interval may be shortened, owing to shortening of the interval between depolarization and repolarization of the muscle mem-

brane with each contraction. This is evidenced by shortening of the refractory period and, therefore, of the QT interval of the electrocardiogram. This is an electrocardiographic equivalent of the physiological phenomenon of shorter duration of ventricular systole under digitalis influence. Wedd and Blair,[55a] working with strips of turtle

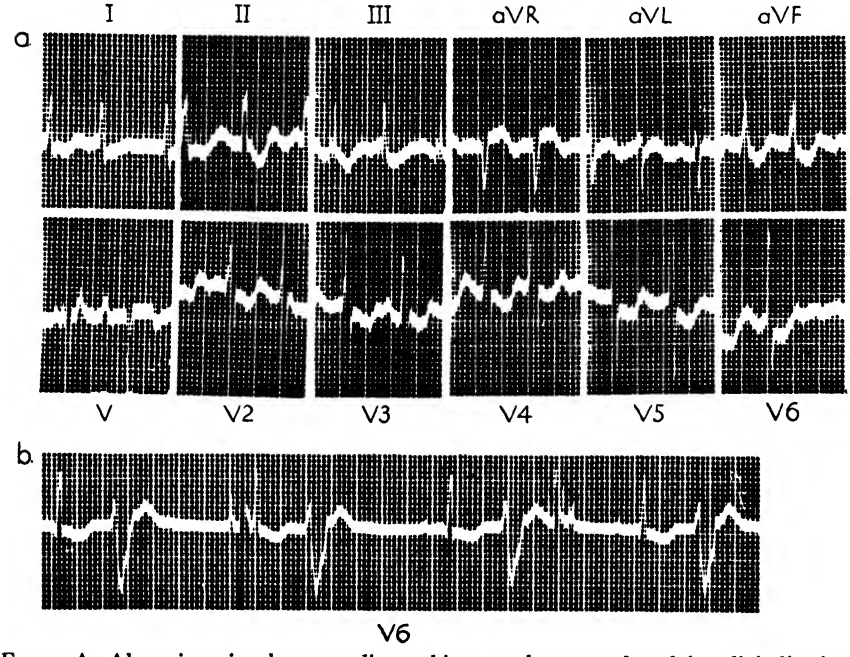


FIG. 4. A. Alterations in electrocardiographic complexes produced by digitalization with folia digitalis. Note the characteristic depression of the S-T segments in practically all leads but lead aVR, where an elevation instead of depression is seen. This effect of digitalis on the S-T segment is not to be considered as a manifestation of toxic action of the drug; it occurs on digitalization with ordinary therapeutic doses. B. Note bigeminy along with the depression of the S-T segments produced by toxic doses of digitalis leaf.

ventricle, have found that a number of digitalis glycosides (digitoxin, ouabain, digoxin, and lanatoside C) were all qualitatively and quantitatively similar with respect to their ability to shorten the QT interval of the electrocardiogram. The magnitude of the effect was proportional to the concentration of the drug.

Delays in auriculoventricular conduction, ranging from the lengthening of the P-R interval to the point of complete auriculoventricular dissociation, are known to be caused by the drug. As the same disturbances of conduction are also produced by myocardial disease, cau-

tion is needed in assigning these changes their proper significance. It may not be possible to make the necessary distinction without stopping administration of digitalis, this being followed by restoration of normal auriculoventricular conduction in case of digitalis effect. If persistent, it can be interpreted to signify myocardial damage, and an indication that less benefit is to be expected from the drug. While atropine may abolish the lower grades of A-V block (such as prolongation of P-R interval), signifying that to a large extent they are due to the vagal effect, higher grades of block may remain unaltered with atropinization, due to the direct action of the drug on the conducting system.

The most characteristic digitalis effect is seen in the deviation and change of contour of the RS-T segments. The deviation consists of displacement below the iso-electric line in one or more leads. This depression may simulate the changes seen in the pattern of the right or left ventricular strain (Barnes). In the standard leads it may assume the shape of a simple concavity, the concavity being directed upward (not infrequently it has a 'scooped-out' appearance); or the RS-T segment may descend at an angle almost as a straight line, starting from the S wave slightly below the iso-electric line. The T wave inversion may occur with or independently of the RS-T changes. Barnes[67] states that 'careful inspection and measurements will show that the T wave is seldom actually inverted. Sometimes it is frankly diphasic, but more commonly measurements will show that the T wave coincides with the limb that ascends from the bottom of the depression (of the RS-T segment) to the iso-electric line.' The RS-T segment and T wave changes may be erroneously interpreted as indicating coronary occlusion.

One should remember that in acute myocardial infarction there are usually Q-waves present; this, however, is not a constant finding.

The confusion between the two conditions is not warranted. More likely, digitalis changes may be confused with the pattern of myocardial insufficiency (Katz), where the Q waves of coronary occlusion are absent and the RS-T segments are not elevated. The characteristic 'scooped-out' appearance of the depressed RS-T segment, where present, makes the recognition of digitalis effect an easier matter.

In the left precordial leads somewhat similar alterations make their appearance, whereas in the right precordial leads an elevation instead of depression of the RS-T segments is sometimes seen. In the unipolar

extremity leads there is also a depression of the RS-T segment in aVL with concomitant elevation in aVR.

The changes in the RS-T segments and the T waves are not affected by atropinization, apparently being due to the direct action of digitalis on the myocardium. The investigators who believe that myocardial effect represents the most important therapeutic mode of action of digitalis cite this electrocardiographic manifestation in support of their theory.

Some light has been shed on the mode of production of the digitalis-induced changes in the RS-T segments by certain investigations. The earliest observations on the occurrence of digitalis injury to the cardiovascular system were in connection with attempts to produce arteriosclerosis in experimental animals. It has been noted that the administration of toxic doses of digitalis results in the appreciable increase in blood pressure, presumably caused by a centrally induced constriction of the arterioles. While some investigators failed to find degenerative or sporadic lesions of the visceral arteries, others (Hueper and Ichinowski) have observed the presence of edematous swelling and hyaline degeneration of the walls of the renal and coronary arteries in cats following repeated parenteral introduction of sublethal doses of digitalis. These authors thought that in the production of lesions in the myocardial vessels not only a vasotonic ischemia is instrumental, but that there is also a mechanical compression of the vascular wall by the prolonged systolic contractions of the surrounding myocardium. This compression would well be expected to reduce and perhaps even temporarily arrest the coronary circulation. Hueper states that these circulatory disturbances in the coronary system causing vascular ischemia and stasis in the myocardium are particularly prone to take place in the subendocardial parts which are supplied by the distal portions of the coronary tree. The prediliction for subendocardial localization of such changes may very well explain the depression of the RS-T segments in the left precordial and aVL leads. In that case one would expect to see concomitantly elevation of the RS-T segments in the aVR and right precordial leads. In fact, such an elevation is frequently observed, more commonly in aVR.

The appearance of premature contractions is sometimes observed in the course of digitalization. The appearance of ' coupling ' or bigeminal rhythm in a patient receiving the drug may be interpreted as indicative of full and even excessive digitalization. Of course, the possibility of underlying myocardial disease being responsible for this

phenomenon should not be overlooked. Here again the necessary distinction can often be made only after the withdrawal of digitalis. If premature contractions disappear when treatment is stopped, digitalis is to blame. On the other hand, their persistence indicates that they arise as a result of heart disease, and in that case may disappear as myocardial function improves on further digitalization. The drug causes premature ventricular contractions more frequently than auricular ones.

Digitalis may cause sinus arrhythmia, tachycardia of auricular or ventricular origin, auricular fibrillation, and ventricular fibrillation. These arrhythmias will be considered later in the discussion of the toxic effects of the drug.

It has been noted that the above-described electrocardiographic changes make their appearance within only a few hours after administration of large oral doses of digitalis, thus testifying to the rather rapid absorption of the drug from the intestinal tract.

Effect on the Clotting Mechanism

It has been recently demonstrated by deTakats and his associates[58,59] in their experiments on dogs that digitalis affects the clotting mechanism. They found resistance to heparin after administration of large doses of the drug. When digitalis is stopped, the reaction of the clotting mechanism to heparin becomes normal. The mechanism of this action has not been elucidated. Several possibilities have been suggested: Digitalis may have thromboplastic properties; it may mobilize prothrombin from the liver, or even increase thrombin or fibrinogen. These investigators believe that the tendency to thrombosis may be increased by the drug particularly when ' pushed beyond a certain point.' They reported cases in which digitalization, embolic phenomena, and changes in the clotting mechanism seem to coincide. They advise to watch the clotting mechanism from time to time in patients receiving digitalis, particularly in those with auricular fibrillation, since here the factor of auricular stasis adds to the hazard of thrombosis.

Massie and his associates[59b] have also demonstrated a reduction in the clotting time in patients who were receiving digitalis. On the other hand, Sokoloff[59c] and Ferrer[59c] have found on determining the clotting time in patients during the course of digitalization that the variance in results due to treatment was less than that due to experimental error. The authors have concluded that their experiments failed to support

the contention that oral digitalization increases the coagulation of the blood. Similarly Puharich and Goetzl[59d] have found that the administration of therapeutic doses of digitalis to patients with uncomplicated heart failure does not significantly affect the coagulation time of blood. However, they have observed that, in cases of cardiac decompensation complicated by the presence of devitalized tissue due to infarction or trauma, the administration of digitalis may increase the danger of thrombus formation and embolism. These authors have suggested that the mechanism of this effect may be due to the release by the drug of an intracellular clot-promoting factor. Haag and associates,[59c] in their experiments on dogs, have noted that the clotting mechanism of the blood was not altered by the administration of digitalis unless given in amounts of 50 per cent or more of the fatal dose, and even then only in certain instances and to a moderate degree, where a barbiturate anesthetic agent was employed (coagulation time may undergo a steady lowering over a period of many hours after the administration of a barbiturate anesthetic). They also failed to demonstrate any antagonism between heparin and digitalis *in vitro*.

Thus, it can be seen from these reports that the question of the effect of digitalis on the clotting mechanism, when administered to patients with congestive failure, still remains unsettled. It has been suggested that the surface active properties of the digitalis glycosides and their saponinic contaminants may play some role in modifying the clotting mechanism by acting upon the surface of the vessels.

Toxic Effects

While in the sixteenth and seventeenth centuries the foxglove was used for its toxic actions as a purge and an emetic, William Withering was the first to distinguish between the therapeutic and toxic actions of the drug. His experience taught him to continue digitalis in moderate doses ' until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects.' This advice has not always been heeded. In fact, the incidence of digitalis intoxication appears to be mounting. Herrmann, Decherd, and McKinley[60] have analyzed the statistics on the incidence of digitalis poisoning among patients admitted to the John Sealy Hospital for the ten-year period 1930–39 and each year thereafter, 1940, 1941, 1942, and 1943. In the ten-year period, from 1930 to 1939, there were only eight cases, an average of about one case a year, as compared with three cases in 1940, six cases in 1941, eleven cases in 1942,

and sixteen cases in 1943. While only one patient in three hundred showed evidence of toxicity in 1940, there was one case in fifty in 1941, one in twenty in 1942 and finally one in every fifteen cases in 1943 exhibited symptoms of intoxication. There was thus a twentyfold increase in poisoning.

Hueper[60a] has summarized some of the toxic aspects of digitalis therapy in a recently published report. He calls attention to the fact that the correct appraisal of the reactions associated with digitalis poisoning may be a difficult matter, at least in some instances, because the symptoms characteristic of digitalis intoxication resemble in many respects those produced by heart disease for the treatment of which the drug is employed. As a result, manifestations of heart disease and digitalis poisoning may be superimposed upon each other.

Gastro-intestinal Tract. The gastro-intestinal symptoms, such as anorexia, nausea, and vomiting, are clinically the earliest symptoms of digitalis intoxication. Not infrequently the patient first complains of a lack of appetite and his tray is returned to the diet kitchen with evidence of loss of interest in food. Later the patient may refuse to accept his tray altogether and when questioned will mention that in addition to having lost his appetite, he now abhors the mere sight of food, which turns his stomach ' inside out.' If full doses are given rapidly, nausea may occur within a few hours of anorexia. Nausea thus soon follows loss of appetite and before long the patient begins to vomit. However, such sequence of events does not always follow, as at times vomiting appears suddenly and in the absence of any previous complaints of anorexia or nausea. This happens particularly during the course of rapid digitalization. It should be remembered that the above-mentioned symptoms may be entirely absent in an over-digitalized patient; therefore, one should not depend on them as the invariable first warning signal and thus allow oneself to be lulled into a sense of false security by their absence. On the other hand, due to passive congestion of the gastro-intestinal tract and the generally poor condition in heart failure, the patient not infrequently will complain of anorexia and nausea even before the beginning of digitalis therapy. The ' seasick ' feeling, weakness, lassitude, apathy, and fullness in the head characterize nausea induced by the drug, while abdominal fullness, pain in the right upper quadrant of the abdomen, and belching predominate in the nausea of heart failure.

William Withering, even though regarding nausea and vomiting as manifestations of direct action of the drug on the stomach, noted

that ' vomiting does not take place for many hours ' after administration. Thus even early in the history of specific treatment with digitalis it was recognized that emesis occurred rather late in the course of digitalization. It should suggest the possibility of other than purely local action.

Emesis occurs with parenteral as well as oral administration, thus precluding the possibility of the exclusive dependence of the gastro-intestinal disturbances on the local irritation of the gastric mucosa. In animals, vomiting movements have been demonstrated, even though the entire gastro-intestinal tract has been removed. Eggleston and Hatcher[61] concluded that digitalis produces nausea and vomiting as a result of direct action on the medullary vomiting center. Their view is not supported by the observations of Hatcher and Weiss,[62,63] who found that direct application of digitalis bodies to the center does not induce vomiting. These investigators failed to obtain emesis in animals after interruption of the afferent nerve pathways which travel from the heart to the medulla. They concluded that the emetic action of digitalis bodies is dependent upon reflexes originating as a result of direct action on the heart.[64] Hatcher and French[65] demonstrated that nicotine abolished the emetic action of the drug, and concluded that the action on the heart, as shown by Hatcher and Weiss, has its origin at the peripheral ends of cardiac afferent nerve fibers. Luten[31] regarded these toxic symptoms as serving as ' a reflex expression of intoxication of the heart.' The fact that usually they occur only after an effect of the drug can be demonstrated in an electrocardiogram was interpreted to signify the cardiac initiation of the reflex responsible for their appearance. However, this concept has been seriously challenged by the recent work of Dresbach and Waddell[66] showing that the drug emetic responses can be induced in the dog in spite of vagotomy, stellate ganglionectomy, thoracic sympathectomy, and spinal cord section at the seventh cervical level, interrupting afferent innervation of all structures below the neck. These studies present a plausible argument also against the view of Hanzlik and Wood,[67] who believed that if it were not the heart, the liver or some other abdominal viscus might be the seat of action. In a more recent report Dresbach[67a] has further extended his previous studies in an attempt to secure more information about the site of origin of the emetic response. He has reported that de-afferentation of the abdominal viscera, total hepatectomy, thorough cardiac denervation, and extensive collective visceral de-afferen-

tation, have all failed to prevent the glycosidic emetic responses. At the same time, however, the injection of nicotine, following complete visceral de-afferentation, blocked the emetic effect of the drug. The author has concluded that his experimental results favored the view that the nausea and vomiting induced by digitalis preparations are mainly of extravisceral origin, most probably central. Pinschmidt[67b] has demonstrated that the vomiting initiated by a cardio-active principle (digitoxin) is not abolished by removal of the carotid bodies and sinuses and by denervation of the aortic mechanisms. He has concluded that: 'assuming the mechanism to be reflex in nature, the site of origin of the impulses causing digitalis vomiting is still undetermined.' The solution of this problem awaits further investigations.

Diarrhea is another means by which the digestive tract can register violent protest against excessive dosage. Abdominal discomfort or pain sometimes accompanies other gastro-intestinal symptoms. They disappear in a few days after the discontinuance of the drug. There is a great variation in individual tolerance and the total dose of digitalis which must be given before these symptoms of toxicity appear. On the average it is the same for normal people and patients with heart disease.

Cardiac Manifestations of Toxic Effect. The toxic effects on the heart may be very pronounced. Some of them resemble different manifestations of heart disease itself.

The effect of digitalis on the conducting system manifested by prolongation of A-V conduction time and higher degrees of block has already been mentioned in the discussion of the electrocardiographic changes produced by the drug. No dogmatic statement is possible in regard to how far advanced this block must be before it can be regarded as an evidence of digitalis toxicity. It will be recalled that one of the objectives sought in administration of digitalis to patients with auricular fibrillation is the production of some degree of interference with conduction. Thus under certain circumstances, the appearance of some degree of block is to be looked upon as one of the therapeutic aspects of drug action. At the same time, however, this effect has been maintained by some to constitute rather a toxic action.[42,68] Certainly the production of complete auriculoventricular dissociation in case of auricular fibrillation can be regarded as a sign of toxicity. In patients with regular rhythm, the prolongation of the P-R interval beyond 0.2 second (if normal before digitalization) has the same significance.

Although it is believed by many that digitalis has no influence on

intraventricular conduction, Wiggers and Stimson[69] record observations that the drug does prolong intraventricular conduction, even in subtoxic doses.

All depressors of cardiac excitability, including quinidine, may cause ectopic rhythms when given in large doses. This is due to reentry of the impulse through blocks of myocardial tissue with lowest excitability. The premature contractions caused by digitalis are most frequently of ventricular origin, although auricular premature beats are also known to arise as a result of digitalis toxicity. The ventricular premature contractions may appear after each sinus beat, resulting in 'coupling' or bigeminal rhythm. The latter, if nonexistent prior to institution of digitalis therapy, is to be regarded almost always as evidence of toxicity, although the possibility of the underlying heart disease being responsible for its appearance should not be entirely dismissed even then.* The existence of ectopic beats in an untreated case is not considered as a contraindication to digitalis therapy. They may result from altered irritability of a failing myocardium and may disappear on exhibition of the drug.

Sampson and his co-workers[69a] have shown that the ectopic beats caused by digitalis can be abolished in every instance by the oral administration of potassium salts. Because in the previous studies by Sampson and Anderson only about 50 per cent of ectopic beats from other causes were affected by the same medication, the authors have concluded that the disturbance of potassium balance in the heart muscle is related to digitalis administration, at least in toxic doses.

The effect of digitalis on the normal pacemaker has already been discussed. It was pointed out that in therapeutic doses the drug may have slight to moderate effect in congestive failure. Large toxic doses can notably depress the sinus node, leading to conspicuous cardiac slowing. Occasionally auricular standstill has been observed to occur.[70] The slowing may also result from a marked effect on the conduction system, resulting in dropped beats. Even complete auriculoventricular dissociation may occur. It is customary to consider the slowing of ventricular rate below sixty beats per minute as an indication for stop-

* Sagall and Wolff (*New England J. Med.*, 240:676, 1949) have attempted to define the characteristics of bigeminal rhythm resulting from digitalis intoxication. They have found that the electrocardiographic features of digitalis-induced bigeminy, as a rule, differed from that spontaneously occurring in subjects with and without heart disease. Digitalis bigeminy was almost always due to premature ventricular contractions, and the premature beats were more likely to be multifocal in origin and to arise in the right ventricle; in no case were they observed to arise from the basal portion of the ventricles.

ping digitalis. However, the change of cardiac rate in the direction of slowing is not the only danger signal. An opposite effect of acceleration may also result from over-digitalization, as is obvious from the discussion of digitalis-induced premature contractions. Therefore, a notable increase in heart rate in a patient receiving digitalis should be looked upon as a possible toxic manifestation.

Sinus arrhythmia is at times observed, but usually indicates only minor toxic action.

Auricular fibrillation is known to appear in the absence of any other evidence of toxicity. It can be mentioned in passing that the production of this type of arrhythmia is the objective sought in the treatment of auricular flutter.

The appearance of auricular tachycardia as an evidence of toxicity also has been recognized. Robinson and Wilson[71] and Cushny[8] have reported that they had succeeded in demonstrating in animals an increase in automaticity of the auricle on administration of toxic doses. It has been subsequently shown in animal experiments that digitalis, by raising vagal tone, can increase irritability and accelerate conduction in the auricles. Auricular tachycardia probably is not due to a center of high rhythmicity. Were this the case, such rhythms would be observed with all rates from ninety beats per minute and up. Hence, most authorities regard auricular (and ventricular) tachycardias as due to re-entry of the impulse through a small focus of lowered irritability.

Ventricular tachycardia is a more serious disorder of rhythm and is cause for alarm, for it may herald the onset of the frequently fatal ventricular fibrillation. Its appearance, therefore, calls for immediate cessation of digitalis therapy. It has been shown that one particular type of ventricular tachycardia is more apt to precede the onset of ventricular fibrillation. It shows an alternate reversal in the direction of the QRS complexes.[72] In most of the reported cases there was evidence present of an underlying grave myocardial disease. Although to most patients large doses of digitalis were administered, in some they were not larger than customarily employed. Just the same, this particular phenomenon may well be regarded as evidence of digitalis effect, for it has almost invariably been found in association with digitalis administration. Death has usually followed the appearance of this rhythm. A modified figure-of-eight circus movement with one center below the bifurcation of the bundle has been advanced in explanation of the bidirectional form of the tachycardia.[73]

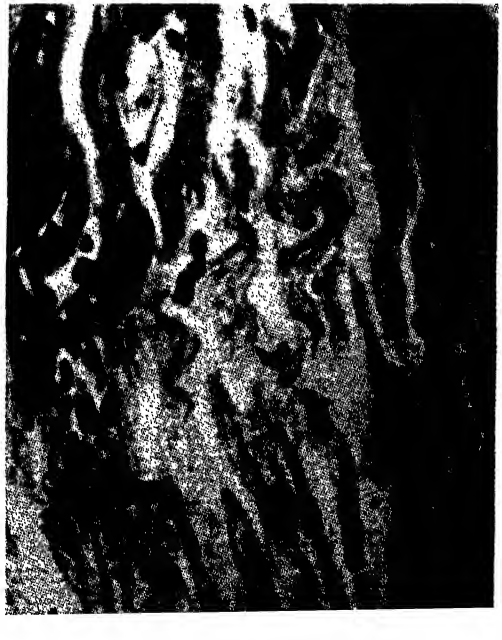
Braun and Wosika[70a] feel that a simple or modified figure-of-eight

circus wave hypothesis is inadequate to explain bidirectional paroxysmal tachycardia. They believe that multiple ectopic foci present in the damaged myocardium are responsible for this disorder. The height of the paroxysm may be the result of interference phenomena, or may follow the predominance of two centers of the same order over the other ectopic foci. The authors were able to demonstrate a selective toxic sensitivity to Digitalis purpurea in the patient who developed this type of tachycardia in the course of digitalization. While the administration of this drug precipitated the tachycardia upon two occasions, strophanthin and Digitalis lanata maintained compensation without producing such toxic effects.

It seems that ventricular fibrillation may appear unheralded by a preceding attack of ventricular tachycardia. It is well known that it occurs as an expression of digitalis intoxication in the course of experiments on animals.[8] According to many investigators the arrhythmia may be the ultimate cause of sudden death in patients receiving large and excessive doses of the drug. An explanation has been offered for the mode of production of ventricular fibrillation, so frequently fatal, in patients who have been receiving digitalis over extended periods of time. It has been shown that after the administration to animals of a sublethal dose and then allowing for varying periods of time to elapse after this initial dose, the administration of a subsequent amount of the drug smaller than that required to kill on the first day led to a lethal outcome.[71] It has been suggested that repeated doses seem to sensitize to subsequent action of the drug, and unexplained death in patients receiving digitalis may in some instances be dependent on such sensitization.

The cardiac manifestations of toxic effect find expression not only in physiological terms of disturbed function, but also in anatomical terms of altered structure. It has been shown by a number of investigators like Lewitzky,[74] Buchner,[75] Weese and Dieckhoff,[76] and others that digitalis produces necrosis and fibrosis in the heart muscle of experimental animals. After the administration of sublethal or lethal doses of digitalis and cardiac drugs to various species, areas of focal necrosis, cellular infiltration, interstitial edema, fibrosis, and hyaline degeneration have been found on microscopic examination of heart muscle, especially in the ventricular musculature, and most commonly in the subendocardial areas. In some sections the muscle fibers show loss of striation, branching and pygnotic nuclei, along with mononuclear and polynuclear cell infiltration. In animals which survived the acute ex-

Fig. 5. Myocardium of a cat after 43 subcutaneous injections of 0.0025 mg/Kg. digitoxin administered at intervals of 48 hours. Duration of experiment 140 days. Killed with ether. Staining: Hemalum-eosin. Magnification: 600X. Extensive or localized focal degeneration with pronounced relaxation and swelling, in places homogenization, of the muscle fibres and loss of cross striation. These areas do not stain well. No inflammatory infiltration, no scars. (From E. Rothlin, *Proc. Rudolf Virchow Med. Soc., City of New York*, vol. VI, 1947, Brooklyn Medical Press, Inc.)



periments, fibrosis was sometimes very marked. La Due[77] found that atropine had a protective action, prolonging the life of the animals injected with the drug, and suggested localized spasm of the coronary vessels as a possible mechanism for the production of myocardial necrosis. Adrenalin had the opposite effect, making animals more susceptible to development of all the various histological changes above described.[78] These investigations tend to affirm the possibility that the toxic effects exerted by digitalis glycosides upon the functional activity of the heart muscle are the result of the myocardial lesions directly or indirectly produced by these drugs and thus represent, after repeated administration of digitalis preparations, ' manifestations elicited by the superimposition of successive anatomic myocardial lesions produced by the individual dose of the digitalis glycosides administered.'[79] This concept of an additive anatomic effect as the cause of toxic symptoms from repeated digitalization is worthy of consideration and presents a new point of view to be contrasted with the older functional-cumulative theory of Hatcher.[80]

The results obtained by some investigators have led them to the conclusion that severe constrictory vascular ischemia is the cause in the production of myocardial lesions. On the other hand, Bircher, Rothlin, and Suter,[80a] as a result of their infusion experiments, have found marked vascularization of the myocardium and increased coronary blood flow in the isolated perfused heart, even after lethal doses of various cardiac glycosides. They have arrived at the conclusion that it is unlikely that the muscular degeneration, found histologically, is caused by circulatory disturbances; a direct effect on the heart muscle fibers is much more probable. Diversity of opinions on this subject is further exemplified by the results obtained by Gilbert and his associates.[80b] These investigators have found that the cardiotoxic effects of digitalis in the dog may be modified by the use of aminophylline, theobromine, sodium acetate, and atropine sulfate. At the same time, papaverine hydrochloride did not minimize the cardiac changes produced by digitalis administration. They have pointed out that the harmful action of digitalis can be assumed to result from the operation of one of three different mechanisms: (1) by direct action of digitalis upon the myocardium; (2) by stimulation of the vagus nerve resulting in the liberation of acetylcholine (which substance produces coronary vaso-constriction); or (3) by a direct action upon the coronary arteries resulting in constriction of these vessels. These authors have felt that since atropine definitely minimizes the cardiac changes

that occurred, the toxic action of digitalis is not a direct one on the heart muscle but is, instead, the result of vagal stimulation, which produces coronary constriction resulting in myocardial ischemia.

Effect on the Skeletal Muscle. It has been demonstrated that the efficiency of a nerve muscle preparation can be markedly impaired by excessive amounts of a cardiac drug added to the perfusing fluid.[8] The possibility of the toxic effect of digitalis on the skeletal muscle in man has been considered. La Due[81] presented a case history illustrating generalized muscular weakness as a toxic reaction to digitalis.

Nervous System. Cerebral manifestations of intoxication with digitalis are encountered. Headache is not uncommon. Confusion and even delirium have been noted, particularly in older patients. Impairment of memory and temporary aphasia have been described. The mode of production of these symptoms is not definitely known. Certain degenerative changes in the brain of experimental animals have been produced by digitalis poisoning. Hueper and Ichniowski[79] report degenerative glial and ganglionic cellular changes. The lesions consisted of vacuolization and disintegration of individual ganglion cells located in the centers of the basal region and in the brain stem. Smaller glial cell infiltrations were found in the cerebellum, while markedly engorged capillaries with focal degeneration of the nervous substance were seen occasionally. In the guinea pig, meningeal and cerebral vessels were markedly congested and the cerebral parenchyma was edematous.

Gold and his associates[81a] have produced convulsions in a rat with a number of different digitalis glycosides (digitoxin, gitalin, and ouabain). They have found that the convulsant action appears to be more highly developed in some (digitoxin) than in other (ouabain) members of the group. They have stated that: 'There is indication that differences in the convulsant activity of different members of the digitalis group are due, in part, to differences in fixation or the speed of elimination, and in part, to differences in the convulsant factor in the molecular structure of the glycosides.'

Batterman and Gutner[81b] have recently reported unusual neurological manifestations of digitalis toxicity. About 9 per cent of their patients suffering from digitalis intoxication exhibited peculiar neurological complaints, such as pain, usually involving the lower third of the face, simulating the syndrome of trigeminal neuralgia. The pain was characterized as a dull aching in the teeth or as a sharp and stab-

bing pain throughout the mandible, maxilla, or both. Other areas involved with typically neuralgic 'shooting pains' were the upper extremities, lower lumbar area with posterior thigh radiation, and calf muscles. Paresthesias, such as tingling in the fingers and burning sensations in the feet, were also observed. The type of digitalis preparation administered apparently played no role in the occurrence of these complaints.

Toxic Effect on Other Organs. Hueper and Ichniowski[79] also report pathological changes in other organs. Thus they describe venous congestion, pulmonary edema, and intra-alveolar hemorrhages in the lungs. In addition, in the liver marked congestion, particularly in the pericentral zones, interstitial edema, and hemorrhages accompanied by hepatic atrophy were observed. In the adrenals, marked congestion and edema, and even hemorrhagic destruction in the medulla were seen. In the testes there was a moderate degeneration of the spermatogenic epithelium. The authors attributed these changes to a relative hypoxemia in the extra-cardiac organs caused by serious circulatory impairment due to the toxic effects on the heart (excessively prolonged and accentuated systolic contraction and an incomplete and shortened diastolic dilatation of the ventricles). There are no corresponding observations available in man.

To conclude the discussion on the toxic effects of digitalis, it should be pointed out that toxicity may be regarded as an extension of therapeutic actions of the drug. Various preparations may differ in degree of toxicity, but an entirely 'non-toxic digitalis does not exist.' [88]

Allergy to digitalis has been reported[82] but it must be rare. White[83] states that he has not encountered an instance 'among a good many thousand cases.'

Absorption and Elimination

It must be conceded that smaller doses of digitalis may be required for producing a certain effect when administered intravenously than by the oral route. The presumption exists that this difference is due to the failure of complete absorption from the gastro-intestinal tract. However, no difficulty is usually encountered in achieving the desired therapeutic result by administering digitalis orally, as long as adequate amounts are exhibited. The requirement of larger oral than parenteral dose may in part be due, as in the case of testosterone or estrone, to some destruction of the drug by the liver through which the blood

from the digestive tract must go before entering the systemic circulation.

The stomach does not participate in the absorption of the active principles, and the drug is absorbed from the small and large bowel. Svec[84] and Brucke[85] have shown that the gastric juice has the property of decreasing the activity of digitalis. Holste[86] found that diastase pancreatin and intestinal juice each decrease the potency of the drug. Hale[87] obtained similar results with artificial pancreatic juice. There are no reports on destruction of the drug in the colon. Evidence for the destruction of digitalis is not conclusive. Robinson[70] states that there is 'no convincing evidence that any of the digestive juices or their ferments have any important destructive action on any of the digitalis glucosides.' Strophanthus and squill constitute an exception to the rule of unhampered absorption from the intestinal tract. The implication of this fact will be discussed in the appropriate chapters.

It has been maintained by some workers that the congestion of the digestive tract in heart failure may interfere with absorption. However, the effective dosage of digitalis appears to have no constant relationship to the degree of visceral congestion, so that this factor seems to be rarely of any great consequence, although it must be conceded that in an occasional instance, possibly due to poor absorption or a combination of factors, the effective oral dose may have to be unusually large.

Absorption from the gastro-intestinal tract, with either oral or rectal administration, is nearly complete within two or three hours, and not later than six.[42,88] The drug seems to disappear from the blood stream very promptly[10] and is in all appearance absorbed or fixed by the different tissues of the body.[10,11] The time of appearance of the earliest manifestation of the cardiac effect after administration of the drug is of course dependent both on the size of the dose and the route of administration. By intravenous route this effect may become apparent in less than an hour, whereas the interval is from two to six hours with oral doses. However, the attainment of a full therapeutic effect may vary from twelve[68] to twenty-four hours.[42] This lag in attainment of full therapeutic results should be kept constantly in mind, as serious consequences of overdigitalization may result from premature administration of successive additional doses. The length of time a given amount of the drug may be expected to continue to exert its action is dependent upon the rapidity of elimination of the active prin-

ciple from the body. This period has been variably estimated from ten days up to two weeks or longer.[42,68] The appreciation of the fact that such latent period exists is necessary if one is to avoid intoxication which may supervene from administration of digitalis in larger than maintenance dosage to a patient who has recently had full therapeutic dose.

It has been found in animals that the drug is eliminated largely by the liver and to a small extent by the kidneys.[42,10] The mode of elimination in man has not been definitely ascertained.*

It was formerly held that the rate of disappearance of digitalis from the organism bore no relation to the rapidity of administration or the amount in the body.[88] It was generally agreed that the average quantity of digitalis eliminated per day ranged from 0.1 to 0.2 gram.[18] This is now known to be untrue. It has been shown rather conclusively that the rate of elimination bears a definite relation to the quantity of the active principle in the body.[89,90,91] A conclusion has been reached that ' patients do not excrete a fixed quantity of digitalis daily, but one that varies with the amount present in the body.'[92] This fact is of great clinical importance, for it has direct bearing on the problem of cumulation and continuous dosage. As an example — the patient may be digitalized by the ' slow ' method of relatively small daily doses, in which case it may be found that on regaining compensation the same daily amount of the drug may be continued as a maintenance dose without producing any toxic effect. This may only mean that at the beginning of treatment the elimination of the drug from the organism must have been negligible, for otherwise an accumulation of amount sufficient for full digitalization effect could hardly be achieved, but with increase

* The experiments on animals by Dr. M. Friedman (personal communication) have demonstrated that the renal elimination of a cardiac glycoside (digitoxin) is nil except when huge doses are employed. This investigator has been able to recover and measure as little as one microgram of digitoxin added to the twenty-four hour urine volume of a rat. Under carefully controlled conditions ten rats were given 100 micrograms of digitoxin per kilogram of body weight (this compares by weight to about 7 mg. dose for a human). The urine collected either the first, second, or third day contained no detectable digitoxin (i.e. less than one microgram per daily urinary output). Thus, with relatively large doses the rats excreted very little, if any, of the drug through the kidneys. When huge doses were administered (1,000 micrograms per kilogram of body weight) to twelve rats, approximately six micrograms were recovered on the average in the urine collected within the twenty-four hour period after the intra-peritoneal injection. It is the opinion of this worker that very little of the drug is excreted by the kidneys of the human subject. However, this conclusion is predicated on the results of the animal experiments and no data are furnished to date on the excretion of the cardiac glycoside in man. In the same laboratory the standards are being set up for detection of the drug in human urine.

in the body content of digitalis the increased elimination allows the administration of the same daily dose without producing toxicity. In other words, the cumulation of the drug in the body tends to be a self-limiting process, at least within certain boundaries.[81] When the treatment is first begun, the rate of elimination is relatively slow, as there is only a small amount of the drug present in the organism. Later in the course of treatment more of the drug accumulates, but at the same time the rate of elimination becomes accelerated. Finally, on reaching a certain level a state of equilibrium is established and elimination equals intake. However, the self-limiting nature of the cumulative process is itself not without limits. The boundary can be transgressed with excessive doses, in which case elimination cannot keep pace with intake and cumulation progresses to a toxic level. The advantages of the cumulative effect and the self-limiting nature of this process lie in the fact that the therapeutic effect can be maintained at a more uniform level than would have been possible were absorption and elimination accomplished with abruptness.[81]

Standardization

Although the different species of digitalis plant all have the same cardiac action, they vary widely in potency. For example, it has been found that D. purpurea is about twice as strong as D. campanulata, while D. alba occupies an intermediate position between the two.[93] For greater uniformity the dried leaf of D. purpurea only is used as a source of the official digitalis preparations. But even within the same species, the different specimens vary in the amount of active principles contained. These variations are conditioned by the locality in which the plant is grown. The age of the plant may also be a factor. In addition, differences in preparation and degree of deterioration are bound to result in change in potency. All these influences are to be taken into consideration and call for proper standardization of the product. The lack of such consideration may lead to notable variations in potency with faulty labeling of the final product in regard to the actual amount of the active principle contained. That proper attention to this problem is not always given by the manufacturer is evident from comparatively recent studies showing rather marked variations in the potency of some of the commercial preparations of digitalis.[94,95] Instances of incorrect labeling have been reported.[96]

The following table prepared by Cattell and Gold[98] gives an illustration of the difficulties encountered:

POTENCY OF TINCTURES OF DIGITALIS (U.S.P. XI)

Specimen	*Cat Unit Potency cc. of Tincture*
John Wyeth	0.35
Parke Davis	0.36
Parke Davis	0.46
Squibb	0.58
Digitol (Mulford)	0.58
Digitol (Mulford)	0.86
Lilly	0.60
Tr. Digitalis U.S.P. XI	0.96

The authors add that 'actually preparations of digitalis on the market show a much wider variation. . . . We found the strongest preparation three times as potent as the weakest, a difference of 300 per cent, although they are all labeled U.S.P. XI.'

Proper standardization of digitalis preparations is thus paramount. Knowledge of the chemistry of Digitalis purpurea is not sufficiently advanced to allow determination of potency by chemical means; therefore, the biological technique has to be employed. Pigeons, frogs, and cats have been used for this purpose. Frogs and cats are the animals generally employed, and more recently cats to the exclusion of frogs. Prior to a recent revision (1942) the U.S.P. official method required that the digitalis be assayed on frogs and that the reference material used be a Standard Reference Digitalis. The strength of the latter is known in relation to the International Standard Digitalis powder. In accordance with this method the tincture of the reference digitalis is injected into the ventral lymph sac of frogs. The systolic arrest of the ventricles in one hour serves as the end point. One U.S.P. Digitalis Unit or International Digitalis Unit is the equivalent of 0.1 gram (1.5 grains) of the International Standard Digitalis powder.

Another technique in use is the cat method (Hatcher and Brody). It consists of the intravenous injection of the drug, the death of the animal in one and one half hours serving as the end point. The authors of the method found that the minimal lethal dose of ouabain (crystalline g-strophanthin) for cats is rather uniformly 0.1 mgm. per kg. They felt that the accuracy of standardization is improved if ouabain is also injected in conjunction with digitalis. First a given amount of the digitalis preparation to be standardized is administered and then ouabain is given slowly until death occurs. By subtracting the amount

of ouabain used from its theoretical lethal dose, the part contributed by digitalis in reaching the end-point is thus calculated. The potency of the tested digitalis is then known in terms of ouabain. The amount of digitalis which is lethal to one kg. of cat is referred to as one cat unit. The cat method of Hatcher and Brody or its modification by Magnus and Van Wyngaarden is commonly used in this country and has been finally adopted by the United States Pharmacopœia (1942). The modification by Magnus consists in employing artificial respiration, which permits the cat to tolerate a much larger dose of digitalis. As a result, the cat unit assayed by this modified technique represents a larger amount of the active principle than does the original Hatcher-Brody cat unit. It so happens that the Hatcher-Brody cat unit represents almost the exact amount of digitalis in 0.1 gram (1.5 grains) of powder or 1.0 cc. of tincture of the original U.S.P. X digitalis. This allowed a ready interconversion between cat units and 0.1 gram (1.5 grains) or 1.0 cc. doses of U.S.P. X digitalis. However, with the change in potency of digitalis preparation through the adoption in 1936 by the U.S.P. XI of the international digitalis powder as the standard, the interconversion between cat units and U.S.P. digitalis units became more difficult. It has been held by some that assays with the cat method are more nearly applicable to man in the case of digitalis leaf than the frog method.[97] However, serious objections have been raised to both. These methods measure the toxic and not the therapeutic effects of digitalis bodies. The assumption is that the toxic activity as measured in the frog or the cat should bear some fixed relationship to the therapeutic activity in man. This might be true provided: (1) All samples of the crude drug contained the several active principles in the same proportions; (2) All these active principles had the same toxic-therapeutic ratio; and (3) All of them were inactivated at the same rate (Moe). The first assumption is generally conceded to be erroneous. That the different glycosides may not possess the same toxic-therapeutic ratio has been demonstrated.[17] The rate of inactivation has also been shown to differ.[98] Thus the ordinary toxicity criterion used in biological standardization is open to question. For the discussion of the latest bio-assay, employing the embryonic duck heart, see Chapter III.

In the attempt to circumvent the difficulties of the 'unphysiological' approach to the problem of standardization more 'physiological' methods have been proposed by different investigators. Thus Hanzlik[99] introduced the pigeon emesis technique. He argued that since

nausea and emesis belong to manifestations of the minor toxicity of digitalis, this method approximates more closely the measurement of a therapeutic action of the drug. In their modification of Hanzlik's method, Haag and Woodley[100] used the minimal lethal dose for the end point. Lehman and Paff[101] introduced the embryonic chick heart as a preparation for the assay. The embryos are dissected and the hearts of desired maturity are selected. The end point adopted is the appearance of a block between the atrium and the ventricles or of dropped beats for the whole heart.

The realization of the importance of study and assay of digitalis in terms of its important therapeutic actions rather than in terms of toxic actions which may or may not be related to any therapeutic effects, led Gold *et al.*[102] to formulate a method for the bio-assay of digitalis in humans. White[88] is of the opinion that this particular technique 'gives promise of advance over the cat method, although it must be noted that human reactions to the drug themselves also vary widely, albeit probably not greatly, in the same individual from time to time.'

Dragstedt[102a] has made a critical analysis of the methods of biological assay of digitalis. He quotes Dale's formulation of certain general principles involved in biological assay procedures. These are as follows: (1) Measurements made by biological means, like every other kind of measurement, must be essentially comparative. No assay has any serious value, unless it is made with reference to an accepted standard. (2) The standard chosen for the comparative test should be, or should owe its activity to, the active principle for which the preparation is to be assayed, and the active principle in question should be that to which the therapeutic value is due. (3) If the test measures the important active principle, the biological reaction employed need have no relation to the therapeutic effect. (4) The method of assay should eliminate or estimate and allow for the inevitable variation in the response of the test object, both the differences in the sensitivity between one individual and another and the variation sensitivity within a single individual from time to time. Dragstedt concludes his critical survey by stating that: 'Conceding, therefore, that the biological assay of digitalis has been a practical success, it must be admitted that this is so, not because the assaying procedures meet all the logical requirements of a significant precision, but because specimens of digitalis probably do not vary as to their glycosidal composition so much as to cause serious difficulty as a rule.'

Because of the time and expense involved in biological assay, along with the considerations presented above, Bell and Krantz[102b] have undertaken, at the suggestion of the Chairman of the Committee of Revision of the U.S. Pharmacopoeia, an examination of the chemical methods available for the assaying of digitalis. The first qualitative chemical test for digitalis glycosides was published by Homolee in 1845. However, the attempts aimed at the quantitative isolation of the active glycosides of digitalis, with subsequent gravimetric and chemical determination, have not proved very successful. Therefore Bell and Krantz have chosen in their work the colorimetric method of Knudson and Dresbach. This method is based upon the Baljet reaction in which a red-orange color is developed by the active glycosides in the presence of alkaline picrate solution. The method was modified by the use of electrophotometer to compare colors. The authors felt that this chemical procedure has proven to give results which agree well with the U.S.P. cat method. In another study by Bell and Krantz,[102c] it has been found that while the color intensities produced by the glycosides of Digitalis purpurea parallel the cardiotonic activity, this relation has not held in the case of the glycosides of Digitalis lanata. Digitoxin was another drug assayed by the same authors.[102d] They also found that this method is less reliable in the assay of tinctures than in the dried-leaf preparations.[102e] The method is based on the presence of an active hydrogen atom in the unsaturated lactone group in digitalis. The reaction is probably not specific and it is possible that sugars may interfere. Further studies have shown that this chemical assay does not measure total biologic activity[102f] and does not yield consistent results.[102g] Anderson and Chen[102h] have investigated the Raymond reaction of *m*-dinitrobenzene with digitoxin. In this test the color reaction is also believed to be caused by the lactone ring of the glycoside. This method has advantages and disadvantages similar to those of the Bell-Krantz chemical assay.

In the course of the last eight years there have been two revisions in U.S.P. Digitalis, one in 1936 and the last one in 1942. The reason for change to a new standard of potency for digitalis adopted by the U.S. Pharmacopœia XI (1936) was to conform with the International Standard. At the Edinburgh Conference of Health Committee of the League of Nations it was decided that ouabain was no longer suitable as a standard for international usage because of the different species of frogs used in Europe for bio-assay and the variety of techniques employed.[103] This was thought to make it practically impossible to get

comparable relationships between ouabain and digitalis in assays carried on in different countries. A powder of digitalis obtained by mixing ten different lots secured from various sources was selected as the standard. However, when this mixed digitalis was assayed on a number of cats, the fatal dose (cat unit) was found to be 83.7 mgm. per kg. cat, instead of the average 100 mgm. required when U.S.P. X Powder (of this country) was used. Thus, each gram of this new reference standard powder contained 11.1 cat units — 11 per cent stronger than U.S.P. X digitalis, 1 gm. of which was equivalent to 10 cat units. Since the International Standard Reference Powder would not be easily procurable by drug concerns in this country, it was necessary to provide a quantity of U.S.P. XI Reference Digitalis Powder. Unfortunately in so doing, a further increase in potency of U.S.P. XI preparations of digitalis over both the old U.S.P. X and the International Standard was brought about. It was found that when a mixture of several lots of digitalis, processed in the United States under the auspices of the Committee of Revision, was prepared to serve as the new U.S.P. XI Standard and then was examined by assay against the International Standard Digitalis, it proved to be stronger than the International Standard.[104]

From clinical observations it has been shown that the increase in potency of the U.S.P. XI digitalis over U.S.P. X ranged from 28 or 30 per cent to as much as 50 per cent.[103] Some biological assays also indicated that the increase in potency was as much as 50 per cent or more.[105] In other words, a pill of 0.1 gm. of whole leaf digitalis equivalent in potency to 1 U.S.P. XI unit was considerably stronger than a pill of the same weight prepared in accordance with the potency equivalent of the older U.S.P. X digitalis. Bland and White[108] state that while in the past they had been accustomed to use one pill (1.5 grains) of U.S.P. X digitalis three times a day for a week with the ' slow ' method of digitalization of an average adult patient, now with U.S.P. XI digitalis they find that 1.5 grains (1 U.S.P. XI unit) given three times a day often has to be stopped on the fourth or fifth day and sometimes even on the third day because of mild gastro-intestinal symptoms or other signs of toxicity. Furthermore, in order to maintain the therapeutic effect with the daily ration of 1.5 grains of U.S.P. XI per day, they found that the drug should be omitted one or more days per week. They recommended that if the physician still wished to think and calculate in terms of U.S.P. X units, that he use one grain pills (0.064 gm.) for the commonly employed 1.5 grain (0.1 gm.) doses.

The U.S.P. XII digitalis unit is to be the activity of 0.1 gm. of an-

other new reference powder and about of the same potency as the present International Standard. Thus it occupies an intermediate position between U.S.P. X and U.S.P. XI preparations, being about 20 per cent stronger than U.S.P. X, but weaker than U.S.P. XI.[106] The indications are that the change may be greater in the tincture than in the powdered leaf.[106] There is then a substantial reduction in the potency to which American physicians have become accustomed in the preceding six years. One grain (0.064 gram) pill of the International Standard strength today (U.S.P. XII) is approximately equivalent to 1⅓ grains of the U.S.P. X digitalis and 0.83 grain of the U.S.P. XI.

The information given above apparently has not been impressed upon the medical profession generally in spite of a number of published articles in the past. Many physicians tend to adhere to traditional and long-established set routines in methods of digitalization based on U.S.P. X or U.S.P. XI doses. Many are unaware of a greater potency by at least one sixth (U.S.P. XII 1942) to one third or more (U.S.P. XI 1936) of the International Digitalis leaf standard over the old standard leaf (U.S.P. X 1926). Also a note must be made of the fact that while some manufacturers increased the strength of their preparations to suit the changes in standardization, others did not. It is incumbent upon every physician employing digitalis to familiarize himself with the potency of the drug he uses and the method by which it was standardized. Carter[107] urges that in view of the wide variations in potency of different products even allegedly assayed in accordance with the one and same standard ' the clinician must depend on the presumably equal potency of the same manufacturer's product. He should urge each patient to use a certain product exclusively.'

In the last analysis it is to be remembered that *there are marked individual variations in response to and requirements of digitalis whatever be its actual potency, and that, therefore, digitalization of each patient is to be strictly individualized. The administration of the drug in each case serves in itself as a clinical assay of the particular product employed.*

Preparations of Digitalis

The preparations from whole leaf of digitalis are available in different forms.

Powdered digitalis, U.S.P. can be administered in pill, tablet, capsule, or suppository form. It suffers little loss of potency with age. No evidence of deterioration has been found at intervals of from one to

sixteen years.[108,109] The administration of the drug in pill or tablet form is most convenient. 'Enteric coated' pills are available for the few who object to the taste of the medication.

Tincture of Digitalis, U.S.P., contains per cc. the amount of active principle equivalent in potency to 0.1 gram of powdered digitalis. Different specimens of the tincture vary in their stability. Generally speaking it is less stable than the powder but the deterioration over a number of years is seldom marked enough to impair its usefulness.[110] In measuring the necessary dose one should avoid the confusion between minims and drops. The usual drop of tincture of digitalis is only one half to one third of a minim. More reliance can be placed on the patient's self-administration of medication in proper dosage if he takes pills or tablets instead of the liquid preparation.

The infusion of digitalis (N.F.) is notoriously unreliable, as it is quite unstable and may undergo rapid loss of potency. It should not be used.

Digitalis leaf suppository (Wyeth) is claimed to contain the equivalent of 15 minims of tincture of 1½ grains of powdered digitalis.

Of the preparations for parenteral use, there are several on the market. Digifolin (Ciba) is labeled as containing in each cc. the amount equivalent in potency to 1.5 grains of digitalis leaf. One ampule of Digalen (Roche) containing 2 cc. is labeled as being equivalent to 1 cat unit. Digalen has been advertised to represent an amorphous and soluble isomer of digitoxin. It is believed, however, to consist mainly of Digitalein Sch. Its administration by vein may be painful and accompanied by thrombosis. Most soluble preparations of digitalis are too irritant for hypodermic injection. Samples of these products have been found to be actually below the expected potency,[94] indicating lack of adequate care on the part of the drug firms in their preparation and labeling. The deterioration of certain aqueous digitalis preparations has been demonstrated. It has been held that the alkalinity of the glass may have something to do with it, and the use of buffer solution as a solvent has been recommended to prevent deterioration.[94]

Methods of Administration

Oral administration is most commonly employed. As the absorption of the drug from the gastro-intestinal tract is rather rapid, the beneficial effects can be expected within a comparatively short time, provided adequate doses are employed.

In case of vomiting, or if for any other reason the drug cannot be

taken by mouth, one can resort to rectal administration, for digitalis has been shown to be readily absorbed from the large bowel.

This route is employed by European physicians more commonly than in this country. Eichorst,[111] in 1916, administered small daily enemas, termed by him 'mikroclysma,' consisting of 5 cc. of lukewarm water, 10 drops of digalen (Cloetta), 10 drops of tincture of strophantus and 0.3 gm. theocin. The usual digitalis effects were noted. Morin,[112] following this lead, used suppositories containing 1 cc. of digalen (equivalent to 0.15 gm. of digitalis), benzocaine, and coco butter. Good therapeutic results were obtained. Employing a solution of sodium iodide, Levy[113] was able to demonstrate that the enema introduced into the rectum finds its way, for the most part, into the distal loops of sigmoid and is absorbed from this portion of the intestine. Lee employed an aqueous solution of extract of digitalis leaves, 1 cc. of the preparation containing the equivalent of 0.1 gm. of powdered leaf, total amounts ranging from 8 to 20 cc. He observed a desirable therapeutic effect in every instance. The average time necessary for an unmistakable initial effect was about two and one-half hours. The dose of digitalis given by rectum was found to be comparable to that usually administered by mouth.

In this country tincture of digitalis or aqueous preparations are used. Since alcohol in the tincture is irritating to the rectal mucosa, the tincture should be diluted (1:7). The dosage is the same as for oral administration. A cleansing enema should be given first. For delivery of the drug a small rubber tube usually employed for rectal anesthesia is quite adequate. Although effective, rectal administration is rather cumbersome.

Intramuscular and subcutaneous injections of digitalis may be irritating. Moreover, in anasarca the absorption is uncertain.

In cases where digitalis is urgently needed because of the grave condition of the patient, the drug can be administered intravenously. For intravenous use the older digitalis preparations have been replaced to a great extent by some of the chemically pure glycosides. Their use for that purpose will be discussed in the chapters to follow.

Dosage

In spite of the warning sounded by Withering against the dangers of overdigitalization, initially the employment of toxic doses was a common practice. At the turn of the century the pendulum swung toward the other extreme of homeopathic dosage. As this, of course, was found to be ineffective, once more the pendulum swung in the

opposite direction, but without quite reaching the extremes of toxicity previously in vogue. Still it did not miss that mark by very far, for it was thought that in most cases the best results could be produced at a level of effect not far below the toxic zone. In other words, the amount of the drug recommended was to approximate that which the patient was able to tolerate. Finally, in the course of recent years, the pendulum came to rest at an intermediate position, expressed by the dictum of desirability to maintain the optimum level of effect, instead of administering as large an amount as the patient could tolerate.

The optimum level of effect from digitalis is ' that level in the therapeutic zone at which the action of the drug results in the highest degree of myocardial efficiency ' (Luten). It has been pointed out that the ability of a patient to tolerate much larger doses of digitalis than are necessary to attain and maintain a condition of optimum improvement cannot serve as a justification for administering larger doses. Although it be conceded that in many cases of congestive failure this optimum level of effect may lie at or near the upper limit of tolerance, in many other instances it may be found at a considerably lower level. Within the limits of the therapeutic zone, the scale of optimum effect is variable. Thus the dose of digitalis required to reach the optimum effect cannot be represented by any fixed amount, as it may differ greatly from case to case. As Luten stated, ' no advantage to the patient accrues from the effect above the optimum level.' No measure of intoxication with digitalis can still further increase myocardial efficiency.

Frequently this optimum level cannot be determined with exactness for the reason that within certain limits variations in doses may fail to produce any demonstrable differences of effect. Still the needed amount in each individual case can in many instances be found by close clinical observation without abusing the patient's tolerance to the drug. However, such abuse cannot always be avoided. It has already been mentioned that in congestive failure the optimum effect of the drug may not be reached except at or near the very top of the therapeutic zone. In these cases it may be necessary at times to overstep the narrow margin between the full therapeutic and toxic actions in order to make sure that no further benefit can be derived from slight increase in dosage. This is then done not because of any expectations of beneficial effect on the myocardium from toxic amounts of the glycoside, but rather due to the fact that in some cases one cannot be certain of having reached the highest therapeutic results without overshooting into the zone of toxicity.

Besides the presence of heart failure and its degree, there are other factors which play an important role in determining the position of the optimum level. Infection may shift it in the direction of smaller doses because of a decrease in tolerance caused by toxins. On the other hand, increase in body weight influences the dosage in the opposite direction, as shown by Eggleston.[120] It appears that the size of the individual is an important factor, the dosage required to reach optimum effect at the same level in different cases varying with body weight. Thus heavy persons require more, while the very thin (and also the elderly) require less of the drug.

All these considerations make it obvious that the proper dosage cannot be determined by rule of thumb. Each case must be judged on its own merits and treated individually. At the same time the physician would be very much at sea were he to depend entirely on his own judgment in deciding how much digitalis may be needed for each individual patient, without first having some conception of the approximate dosage. A working basis is needed to enable the physician to have a plan of attack for the particular problem facing him. This working basis would formulate some concept of the probable optimum dose for an average patient. The average amount of digitalis which may be expected to give the best results must be modified in accordance with the special circumstances of each individual case, but just the same, it allows the formulation of a tentative dose to be employed, thus furnishing a practical basis for beginning the treatment.

Eggleston's work[120] has provided a formula for such tentative dose and the validity of his findings has been confirmed by a number of prominent clinicians. Eggleston found the average total dose necessary to produce full therapeutic or minor toxic effects to be 0.146 cat unit per pound of patient's weight. This amounts to 14.6 cat units per hundred pounds or about 22 cat units for an average patient weighing about 150 pounds. This is equivalent to approximately 30 grains of U.S.P. X digitalis or 23 grains of U.S.P. XII digitalis. It corresponds to 20 cc. of U.S.P. X tincture or 15 cc. of U.S.P. XII. For an adult of average size (weighing between 125 and 175 pounds), the desired therapeutic effect is obtained by an amount varying from 1.0 gram or 15 grains to 1.5 grams or 22.5 grains of U.S.P. XII.[88] In terms of U.S.P. XII tincture, the dose is from 10 to 15 cc. The total amount required depends on the time allowed for complete digitalization. Less of the drug is needed if digitalization is accomplished in a twenty-four hour period, than if it is stretched over the course of a week.

In accordance with the recommendations of the Council of 1924, the total dose may be given within thirty-six to forty-eight hours in the following manner: It may be divided into several equal parts given every four or six hours; or one-third to one-half of the total calculated dose may be given at once, and the remainder in two portions, at intervals of four to six hours. It is a good policy to use a smaller fraction as the total dose is being approached, so as to take into account the factor of variability in the individual tolerance of and requirements for digitalis and thus avoid toxicity. It should be noted that lightweight adults can require more digitalis than indicated by the weight formula, not infrequently one and a half to two times as much.[83] Children can best receive their dosage as indicated by weight.[121]

White[88] makes the following recommendations regarding the procedure of digitalization (the dosages are in terms of U.S.P. XII): 'If there is considerable urgency, the leaf can be given in the dose of 0.3 gram (three pills of 1½ grains or 0.1 gram) every eight hours for three doses (equivalent to 3 cc. of tincture every eight hours for three doses); if there is less urgency but need of saturation in less than a week, 0.2 gram (two pills of 1½ grains each) can be given three times a day for two days or 0.13 gram (two pills of 1 grain, 0.06 gram) three times a day for three days (equivalent respectively to 2 cc. of the tincture three times daily for two days or 1.3 cc. three times daily for three days). If there is little or no urgency and the patient is an ambulatory case and conveniently seen once a week, as in a hospital out-patient clinic, the drug can very satisfactorily be given in the dose of 0.1 gram (1½ grains) three times a day after meals for four or five days, or of 0.06 gram (one 1 grain pill) three times a day (after meals) for one week (equivalent to ⅔ cc. or 10 minims, not drops, of the tincture three times daily for a week).'

It is important to know that while some patients may require only half of the median dose, others may need twice the median dose. With this in mind, Dock recommends beginning with one-half of the latter. He considers the median dose as 20 cat units for a 150 pound man, 15 cat units for a 200 pound man. One-half of this amount is given at first. Eight to twelve hours later the patient's circulatory status is evaluated again with regard to response to digitalis given initially. At that time he gets not more than 25 per cent of the total dose. Each successive dose is ordered after seeing the patient. No more than 1.5 cat units are ordered on a q.d. basis until the patient has been receiving it for at least ten days, but extra doses may be prescribed one at a time while

working up to the required dosage. Each physician can work out his own scheme somewhat similar to those above described.

For rapid digitalization in the treatment of emergencies, the intravenous route of administration can be used. The employment of any but pure glycosides parenterally is no longer considered acceptable. For that purpose strophanthin, digitoxin, digitaline (Nativelle) and lanatoside C may be used, as they are all effective.

In view of the fact that digitalis is not retained indefinitely in the organism, but is gradually eliminated, in order to maintain the optimal effect once obtained it becomes necessary to continue with the administration of the drug in amounts approximating the rate of elimination. It has been pointed out already that the drug is not disposed of in any fixed amounts, but that the rate of elimination, among other factors, is dependent upon the total quantity of the active principle present in the body. Thus not only the total effective dose used for the purpose of saturation, but also the maintenance dose is a matter of individual differences. Here again a working basis has been provided for guidance. It furnishes an average maintenance dose subject to change in accordance with the special circumstances of the individual case. It has been estimated to be somewhere around the figure of 1.8 grains of U.S.P. Digitalis X (or 1.3 grains of U.S.P. XII). According to White[88] it varies from 1 to 1.5 grains for the average adult. It may be added here that the drug has no habit-forming qualities and does not lose its effectiveness from continuous use. In preventing subsequent attacks of heart failure in patients who have recovered from an initial attack, digitalis therapy is of great value, as has been established by Gold and DeGraff.[122]

In conclusion it can be said that ' digitalis dosage is accurately to be measured not in terms of the weight or volume of the preparation employed, nor indeed in biological units, but in terms of the effect produced ' (Luten).

Clinical Applications

Congestive Heart Failure

Of the therapeutic indications for the use of digitalis, heart failure stands first. While Withering introduced the drug as a remedy for cardiac dropsy at the end of the nineteenth century, and Mackenzie inaugurated the modern era of digitalis therapy some forty years ago, it is only in the course of the last twenty-five or thirty years that a

clear understanding of indications for treatment with digitalis has been attained.

Withering used the drug on purely empirical grounds, although with success. Mackenzie was well aware of the fact that the relief of signs and symptoms of failure was secondary to the action of the drug on the heart, but failed to realize all the broad implications of this action. His observations on the remarkable slowing of cardiac rate in auricular fibrillation tended to focus everyone's attention on this particular manifestation of digitalis effect and hypnotized the physicians of his period into the belief that cardiac slowing was the only significant mode of action of the drug. This one-sided enthusiasm went so far as to lead to an assertion that only in cases of heart failure with auricular fibrillation could any beneficial results be expected from the exhibition of digitalis. Limitation of the therapeutic application of the drug to patients with this particular type of arrhythmia remained in force for some time, until other circulatory effects of the drug were brought to light by clinical studies. In this connection a brief review of certain facts regarding failure of circulation will be appropriate.

In patients with congestive failure and normal rhythm, sinus tachycardia is not at all an uncommon occurrence. It is well known that the failing myocardium is unable to sustain a normal stroke volume. In the light of this knowledge, the tachycardia may well be regarded as a result of a compensatory mechanism.[81] It is possible that not only the tachycardia of sinus origin but also the rapid rate in auricular fibrillation may result from such compensatory adjustment. The opinion of some investigators[114,115] is that the stretching of the auricular muscle due to increase in intra-auricular pressure in congestive heart failure may initiate the circus movement. Under such circumstances the arrhythmia appears to be a result rather than a cause of failure. The same conclusion has also been reached by others[116] through the clinical observation that in some cases of congestive failure extended over long periods of time, the initiation of arrhythmia is subsequent to cardiac decompensation.

In cardiac decompensation with auricular fibrillation, the ventricular slowing brought about by digitalis may not be due solely to the action of the drug on the conducting system, resulting in interference with the transmission of the auricular impulses through the junctional tissue. In addition it can be secondary to a decrease in myocardial excitability from the direct effect on the heart muscle leading to greater

efficiency and thereby to relief of partial anoxemia of the failing heart. The slowing of cardiac rate ensues upon the exhibition of digitalis to patients in failure with regular rhythm as well as with auricular fibrillation. While in the first instance it is caused by direct action of the drug on the heart muscle leading to better efficiency, in the second instance the combined effects on conducting tissue and myocardium are operative.

It is obvious that digitalis is indicated in heart failure irrespective of rhythm. In the course of the last twenty-five years the extended studies at the bedside by a number of noted clinicians have unmistakably demonstrated the validity of this postulate. The conviction that congestive failure, regardless of rhythm, is relieved by proper digitalization thus has become firmly established. Now it is a matter of common knowledge and is no longer a subject for debate.

The appearance of a patient in an advanced stage of cardiac decompensation with dyspnea, orthopnea, cyanosis, engorged cervical veins, tachycardia, enlarged heart, basal rales, palpable and tender liver, and swollen limbs is familiar to all. The dramatic relief of all these signs and symptoms by digitalization is well known to the physician. However, the exhibition of an agent so beneficent in its effects must not be limited to patients in far advanced failure. Decompensation in the absence of conspicuous and prominent manifestations is also amenable to digitalis therapy. One should not wait for the appearance of such manifestations before starting treatment. The patient may complain only of breathlessness on effort or smothering spells at night (paroxysmal nocturnal dyspnea). These are symptoms of beginning failure and if left untreated will progress to produce the full-blown picture of severe decompensation. The latter may be prevented, or rather postponed, by the early administration of the drug. It is not good practice to withhold treatment just because more obvious and marked evidence of failure has not become apparent. As soon as it is seen that these symptoms are due to a heart affliction and not some other condition (pulmonary disease for example), the therapy should begin. Greater tolerance to exercise and also such objective findings as improvement in vital capacity will bear testimony to the value of timely treatment. One should also keep in mind that tachycardia may be the only manifestation of a beginning failure in its ' occult ' stage. However, one should make certain that tachycardia is the result of heart failure, for a fast pulse from other causes (peripheral vascular collapse, fevers, etc.) will not be affected by digitalis.

Thus the inestimable value of early treatment has been well established beyond any doubt by competent observers. Some, however, go even a step further and advocate the prophylactic use of digitalis in patients with heart disease and without failure, but in whom decompensation might well be expected to occur. Christian[117,118] states that in cases of cardiac enlargement with hypertension or valvular disease digitalis is of definite value in warding off future decompensation. White[88] seems to agree with Christian on this aspect of digitalis therapy. It may be that in some of these cases thus benefited, ' occult ' heart failure is present at the time the treatment is started. Cardiac enlargement is in itself a sign of beginning failure. Hypertensive patients may have hearts of normal size for decades.

In cardiac decompensation following a recent myocardial infarction, digitalis is as well indicated as in other instances of decompensation. However, in this condition special care should be exercised in avoiding digitalis toxicity. Patients with myocardial infarction may have diminished tolerance to the drug. Bellet and Schecter observed it in dogs during the acute stage of myocardial infarction. This should not serve as a deterrent to the judicious use of digitalis when indicated.

Askey and Neurath,[118a] in their analysis of thirty-two patients in congestive heart failure with myocardial infarction and auricular fibrillation, have found that digitalis alone proved to be more harmful than beneficial. They have observed that the production of fatal ectopic ventricular rhythm with sudden death and cardiac rupture — particularly the first one usually considered as the greatest hazard — did not present significant problems in their series. The mortality was found to be increased largely by the production of fatal emboli to the greater circulation. On the basis of these data, they have concluded that digitalis administered alone for congestive failure associated with auricular fibrillation and myocardial infarction would be contraindicated.

In another study by the same authors[118b] on a series of eighty-four patients with auricular fibrillation, they have noted that although sudden death occurred if no medication was given, or if digitalis alone or quinidine alone was given, death occurred in none of the patients given both digitalis and quinidine. In the group with no congestive failure, quinidine alone gave better results than no medication or digitalis alone. In the patients with congestive failure the worst results were from digitalis alone. In this group 96 per cent of the patients died;

thirteen of these were due to emboli to the greater circulation. The best results were from combined digitalis and quinidine. In the group of patients who received both drugs there was the lowest mortality, the greatest incidence of return to sinus rhythm, and no sudden deaths from embolism. They have felt that the incidence of fatal emboli associated with the use of digitalis alone in the patients with congestive failure was too high to be explained on the basis of chance alone. These authors have considered early elimination of the auricular fibrillation advisable in view of the correlation of the increased incidence of fatal systemic emboli with the prolongation of the arrhythmia. The risk of embolism apparently has not been in reverting the auricular fibrillation to sinus rhythm but in allowing the auricular fibrillation to persist. They have also felt that on theoretical grounds the simultaneous administration of digitalis and quinidine is advisable because both drugs act as buffers against each other's action tending to induce an ectopic ventricular rhythm. Digitalis is capable of inducing paroxysmal ventricular tachycardia, an arrhythmia that quinidine can prevent; conversely, digitalis is believed to prevent ventricular tachycardia arising from the use of quinidine in the treatment of auricular fibrillation.

Heart failure, even when found in association with angina pectoris, calls for the drug (angina is not in itself an indication for digitalis therapy). There is some prejudice against the use of digitalis in patients suffering from angina, for it is believed by some investigators that digitalis may precipitate anginal attacks.[49] However, it has been shown in the course of careful studies[51] that this presumption is not entirely warranted. Since failure often obscures angina, the relief of one disorder may accentuate or unmask the other.

Although the best results are achieved in heart disease on a degenerative or hypertensive basis, quite satisfactory also is the treatment of decompensation secondary to valvular heart disease. In regard to the latter group, aortic insufficiency of luetic origin may in many instances constitute an exception. Digitalis will probably help when decompensation first sets in, but for a shorter period of time than in other conditions; for having once decompensated, the course in these patients is unrelentlessly and rather rapidly downhill. In treatment of failure of rheumatic heart disease, the best response to digitalis and the better immediate prognosis is seen in patients with mitral stenosis alone.[119] According to Flaxman this holds true regardless of whether the rhythm is regular or irregular.

The objective sought is the relief of symptoms and signs of failure. This end is attained to the great satisfaction of the cardiac sufferer as well as of the physician himself in a great many cases. Unfortunately there are some patients with whom it is impossible to achieve this optimum effect.

Once the patient in congestive failure has been digitalized, it is probably best to continue administration of digitalis in maintenance doses. Reference has already been made to the investigations by Gold and deGraff showing that in auricular fibrillation digitalis must be continuously maintained to prevent recurrences of failure. It is commonly believed that digitalis should also be of value in preventing cardiac failure in patients with regular rhythm. Sokolow and associates[122a] have presented objective data in support of this concept. Ambulatory patients with sinus rhythm, who had previously shown congestive heart failure, were studied for periods varying from 31 to 60 weeks. Each was kept on a comparable controlled regime of activity, the only variable being the administration or omission of digitalis. In every instance cardiac failure occurred when digitalis was withdrawn. The authors have concluded that: 'It is unwise to omit this drug in patients with diminished cardiac reserve who have previously shown failure, even though the patient is free of symptoms.'

Although enthusiasm in the treatment of heart failure with digitalis is well justified, it should not lead to the abandonment of discriminative judgment and thus result in the application of the same method of therapy in a field where it is of no avail. Digitalis is not indicated in all cases of cardiac decompensation and congestive failure. The determination of these exceptions is related to the consideration of the etiology of failure and will now be discussed briefly.

The congestive phenomena of constrictive pericarditis could hardly be expected to be amenable to digitalis therapy for obvious reasons. True enough, the cardiac output is diminished and along with it venous congestion may be present which resembles the picture of the 'garden variety' of heart failure. But in cases of this type the cardiac output is decreased not necessarily by virtue of any intrinsic myocardial weakness, but rather for purely mechanical reasons. The organ is bound by constricting adhesions hampering the ejection of blood from the chambers, and the knife of a skilled surgeon by freeing these adhesions will do the trick the drug could never accomplish.

In myxedema, heart failure, although rare, is known to occur. Oc-

casionally even a far advanced stage of decompensation may be encountered.[123] When present, in its clinical manifestations it is similar to myocardial insufficiency from other causes. In this instance thyroid extract instead of digitalis is indicated for rehabilitation of circulation as well as for general improvement.

The breathlessness, cardiac enlargement, with tachycardia and gallop rhythm, engorgement of the lungs and liver, and peripheral edema of a beriberi heart may well simulate a picture of degenerative (arteriosclerotic, hypertensive) or valvular heart disease in the decompensated state. Here, however, in addition to the myocardial changes of metabolic nature due to avitaminosis and resulting in cardiac insufficiency,[124] there is also present a remarkable peripheral effect of arteriolar dilatation. In the latter respect the condition resembles that of arteriovenous fistula. A history of dietary deficiency, warm extremities, and increased velocity of circulation (instead of slowed circulation as in heart failure from other causes) helps in diagnosis. Again digitalis is disappointing, while thiamine will give satisfactory results (but not in all patients).

Recently there has come to general attention a heart condition also possibly secondary to avitaminosis, but not amenable to vitamin therapy, presumably because of its chronicity. Pathologically it also differs from the ' classical ' beriberi heart. Diffuse fibrosis of the myocardium is found, particularly in the subendocardial areas, along with diffuse or patchy endocardial thickening and thrombus formation. Here again digitalis usually fails, although an occasional patient may respond favorably, at least temporarily.[126]

It appears that the drug is useless in cardiac decompensation in patients with scleroderma. According to some investigators[127] in generalized scleroderma the heart along with other visceral organs may be involved. Some evidence has been presented to the effect that none of the common etiological factors contribute to the heart failure in these patients. Scars of unusual type involving the myocardium are described in the autopsied cases.

Arteriovenous fistula of sufficient magnitude and duration can produce cardiac decompensation. It is obvious that an operation closing the abnormal communication rather than digitalis will strike at the root of the trouble. However, digitalis may be used in preparation of the patient for the operation.

Cardiac enlargement, congestive failure, and arrhythmia occur in thyrotoxicosis. Auricular fibrillation is more common in cases of con-

gestive failure. Naturally, therapy directed toward correction of the underlying metabolic disorder is paramount and constitutes the first consideration. Preparation with iodine and then thyroidectomy may in themselves be sufficient for relief of the heart trouble; at least they are far more effective than digitalis. However, digitalis may be tried in conjunction with Lugol's solution as preparatory to surgical intervention. It frequently is ineffective.

It has been pointed out that the presence or absence of infection is of great importance in determining the expectations one may entertain in regard to the efficacy of digitalis therapy.[91] The original impression that the presence of infection or toxic conditions in general (thyrotoxicosis for example) may render digitalis impotent has been well borne out by subsequent observations. Rheumatic fever constitutes one notable example. In the course of an active rheumatic process, the heart failure does not always respond satisfactorily to digitalis therapy.[91] This may be responsible for some of the unfavorable reports regarding treatment with digitalis in children, as it is particularly in this age group that rheumatic heart disease is prevalent and active rheumatic infection is predominantly manifest. However, digitalis should be tried in every case of decompensation occurring in the course of acute rheumatic process, as in some patients the results are brilliant.

A few comments with regard to some concepts of congestive heart failure, including the implications that such concepts may bear on the problem of digitalis therapy, should be made at this time.

Edema is one of the prominent features of congestive failure involving the systemic circulation. In order to understand the pathogenesis of this edema one must recall the classical studies of Starling, who has shown that the motions of fluid between the blood capillaries and the adjacent spaces (extracellular fluid compartment) are governed by the balance between two opposing forces, hydrostatic and colloid osmotic pressures. The force driving fluid from the capillaries into the tissue spaces surrounding them is the hydrostatic (blood) pressure within these vessels; the force drawing water back into the blood capillaries is the osmotic pressure of the proteins (especially albumin). The mechanisms involved are somewhat more complicated. The equilibrium between the blood and extracellular fluid is dependent upon the following factors: the escape of fluid from the small blood vessels into the tissue spaces is favored by capillary blood pressure and colloid osmotic pressure of perivascular fluid and is opposed by colloid

osmotic pressure of plasma and by tissue tension. The inherent lack of elasticity of tissues and distention of tissues by fluid are responsible for the tissue tension mentioned above. On the other hand, the exchange of water between the extracellular fluid and the cells is probably controlled mostly by the osmotic pressure of electrolytes in the extracellular fluid. Among the electrolytes that determine the osmotic pressure in the extracellular fluid the concentration of sodium ion is the most important element. Within the cells it is the potassium, instead of the sodium, which controls the osmotic pressure of the water. The relative proportions of extracellular and intracellular fluid are dependent upon their relative osmotic pressures. These pressures are controlled by the concentrations in the two mediums of the osmotically active components to which the cellular membranes are impervious. These are mainly sodium and potassium. The most important of the two is the sodium in the extracellular fluid. When the concentration of sodium drops the cells swell with water. When the concentration of sodium rises the cells give up water to the extracellular spaces.

The prevalent theory of heart failure implies that in heart failure the venous pressure becomes elevated because blood is dammed up in the venous system owing to the impaired ability of the heart to expel blood from its chambers. The edema presumably occurs primarily as a result of this increase in venous pressure accompanied by increased capillary permeability resulting from stagnation and anoxia. The passive congestion that follows closely on the heels of increased venous pressure results in impairment of filtration though the congested kidneys, leading to retention of salt and water.

Warren and Stead[127a] have challenged the above-presented concept. As a result of their studies on fluid dynamics in chronic congestive failure, they have come to the conclusion that the disturbance in renal function leading to abnormally low excretion of salt and water is related to the decreased cardiac output and not to engorgement of the kidneys from an increased venous pressure. They have observed the salt and water retention occurring before there was a rise in venous pressure. The increase in plasma volume, which is thought to occur in congestive failure, is a manifestation of the retention of salt and water. In due time the increase in the blood volume and the extracellular fluid volume (occult and clinical edema) causes a rise in the venous pressure. The osmotic pressure of the plasma proteins and the increased pressure of the extracellular fluid provide the physical forces

that enable the large plasma volume to be maintained, even though there is a high capillary pressure which results from the high venous pressure. In other words, the sequence of events is as follows: the failure of the myocardium results in decreased cardiac output, which in turn leads to the smaller amount of blood flowing through the kidneys. Consequently, smaller amounts of water and salt than normally filter through the glomeruli and both are retained in abnormal amounts (for the reason that the diffusion of salt and water from within the lumen of the renal tubules back into the circulation proceeds in a normal fashion). Retention of salt and water leads to increased plasma volume and increased pressure within the veins and capillaries. This causes transudation into the tissue spaces, giving rise to occult or clinical edema (see Fig. 6).*

Peters[127b] questions Stead's theory. Among other things, he points out that the methods usually employed for estimation of blood volume may not be valid in patients with congestive heart failure. At any rate, whatever the exact pathogenesis of failure may be, the water and salt retention play a prominent role in the picture.† This has prompted some investigators to lay more emphasis on the employment of diuretics rather than digitalis in the treatment of cardiac decompensation. It must be admitted that digitalis often fails in alleviating the symptoms and signs of passive congestion and that cardio-active principles cannot be relied upon as sole medicinal agents. The extreme of this view is presented by Gold and his associates.[127c] As a result of their studies, they have placed agents for dehydration (the mercurial diuretics and salt restriction) in the first rank among measures effective in the control of congestive failure. In their experience, patients with

* The fact that increased venous pressure may in itself be responsible, at least in part, for the retention of salt and water, has apparently been disregarded by Warren and Stead. It has been known for many years that the obstruction to the venous outflow of the isolated kidney can also diminish the output of salt and water. Thus, in addition to a reflex diminution in renal blood flow due to decreased output by a failing heart, renal venous hypertension also plays a role in producing retention of sodium, resulting in hydremia.

† It is interesting to note that in acute glomerular nephritis (possibly also in other stages of this disease, such as the nephrotic syndrome) the same sequence of events may be taking place as in congestive heart failure in accordance with Stead's concept. Thus, the cycle – salt retention, increase in blood volume, transudation, edema – has also been observed in acute nephritis, even with increase in venous pressure (Luetscher). Here, salt retention is caused by the intrinsic renal disease instead of 'forward failure.' In spite of increased venous pressure, signs and symptoms of cardiac decompensation are not encountered, but there are exceptions; some patients with acute nephritis develop heart failure.

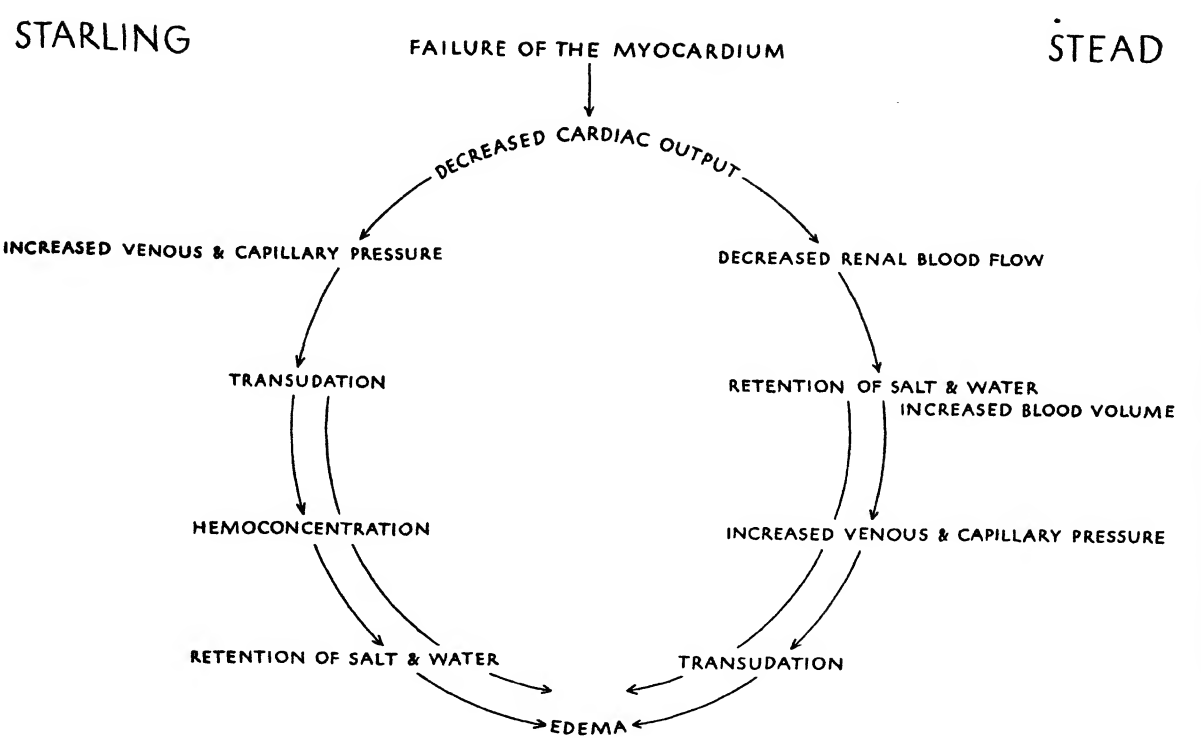


FIG. 6. Schematic representation of the two theories of cardiac edema. (Even when the cardiac output is greater than normal, as in beri-beri heart, anemias etc., it still is *inadequate* for the needs of the organism).

predominantly left heart failure do not respond nearly so well as those with right heart failure. They have emphasized the fact that the patients with sinus rhythm do not respond to digitalis nearly so well as those with auricular fibrillation; the number of patients with congestive failure and sinus rhythm in whom digitalis exerts no conspicuous effect is quite impressive. They have stressed the fact that diuretic agents are not only helpful in accelerating recovery when digitalis alone may suffice after a more protracted course, but that these agents alone, when effectively applied, control the congestive failure in many patients who cannot be improved by the administration of digitalis. It appears that these authors are impressed by the evidence presented above, showing that the immediate cause is a disorder of salt and water excretion. As a result of their observations, they have stated that: '. . . the supposition that the sequence employed in the most common practice of trying digitalis first and then adding a diuretic, if necessary, is in need of revision. In the concept of treatment the indications are that the order should be reversed; an effective technic for dehydration with salt restriction, free supply of water and a potent diuretic become the base of the system; digitalization becomes an auxiliary or accessory measure, without value in many but of some use in others, and essential in a certain group, especially those with auricular fibrillation.' At this point it should be mentioned that, as a result of recent studies,[127b] it has been shown that in some patients with heart failure the serum sodium may be subnormal. If retention of sodium were the primary event in heart failure, serum sodium in this condition should be regularly elevated or at least in the upper-normal range. Apparently, exceptions to this rule occur, and in the group of patients who present such exceptions the administration of salt, rather than restriction, is to be advocated. The author of this monograph agrees with Gold and his co-workers that there are many instances when digitalis is impotent and that in such cases a great reliance must be placed exclusively on salt restriction and diuretics. However, he cannot subscribe to the extreme view of these investigators.

With regard to the question of the employment of digitalis, diuretics, and salt restriction in patients with cardiac decompensation, it will be appropriate to refer also to the recent studies by Stead *et al.*[24b] These authors have classified the cardiac output in congestive failure as follows: (1) The output is low on the patient's admission to the hospital. In such a patient compensation results entirely from the use of salt restriction and mercurial diuretics. If placed on a normal diet,

the patient will develop edema. (2) The output is low on the patient's admission to the hospital but increases on digitalization. Compensation occurs without the use of salt restriction or diuretics. (3) The output is normal on the patient's admission to the hospital, and it remains normal while he is confined to bed. Although adequate for the resting state, it becomes inadequate on effort or in the presence of infection. The symptoms on admission to the hospital presumably have resulted from passive congestion which occurred during activity or have been precipitated by infection. With reduction of activity or clearing of infection, the output is adequate at rest and, therefore, signs and symptoms disappear as long as the activity is markedly restricted. (4) The output is high on the patient's admission to the hospital, and it falls with compensation. Apparently, the cardiac output is increased over the normal resting-level because of anxiety, discomfort, or some associated condition, such as arteriovenous fistula, anemia, or vitamin deficiency (beri-beri). While being higher on the normal basal level, the cardiac output, however, is not high enough to meet the needs of the organism. If the demands of the body for blood are lower, the cardiac output at rest decreases as compensation occurs.

Stead points out that the results from rapid and slow digitalization would cause no confusion in groups 1, 2, and 3. The findings in group 4 will differ by the two methods. 'If a restless, apprehensive patient with moderate failure is studied, the output on his admission to the hospital may be high if digitalization is rapidly carried out. The fact that the output is still not high enough for the state of the patient will become obvious as the output rises to a still higher level with digitalization. Since the output is now adequate for the means of the patient, the signs and symptoms of congestive failure will disappear. The patient loses his restlessness and apprehension, and the requirement of the body for blood decreases. The cardiac output therefore falls. The higher output on his admission to the hospital was inadequate for body needs; the lower output is now adequate, and the signs and symptoms of congestive failure do not recur.' These authors have pointed out that the initial rise in cardiac output incidental to administration of digitalis may be completely overlooked unless observations are made within a short time after the effect of digitalis has occurred. They have stated that similar results are seen in patients with cardiac failure associated with severe anemia. The output is high but not high enough for the body needs, resulting in failure. Whereas digitalization causes a further rise in output, with the correction of ane-

mia the cardiac output falls below the level present before digitalization.*

Cardiac Arrhythmias

In the days when the effect on the conducting system was considered as the sole mode of action of digitalis instrumental in relief of congestive failure, the presence of conduction defects in untreated patients was thought to be a contra-indication to digitalis therapy.[128] In later years, with the recognition of other actions of the drug on the heart, it was accepted that the indications for treatment are dictated by the functional state of the myocardium, irrespective of the state of the conduction system. In other words, patients in heart failure should be treated without regard to the presence of A-V block, partial or complete. However, the presence of A-V block, serving as an indication of serious and extensive myocardial damage, makes for graver prognosis and lessens the expectations of successful therapy. What has been said above in regard to A-V block is also applicable to cases with intraventricular conduction defects. The finding of intraventricular and bundle branch blocks is not an infrequent occurrence in congested cardiac patients, and their exclusion from the group treated by digitalis would be entirely unwarranted. It should be mentioned that the Adams-Stokes syndrome introduces a complicating factor, for such seizures are known to be produced during periods of transition be-

* Apparently failure can occur with either a high or low cardiac output, although most often it occurs with the latter. By application of cardiac catheterization a better understanding of the cardiac output in congestive heart failure has been obtained. As a result of these studies, cardiac failure has been divided into two groups, those characterized by a low cardiac output and those with a high cardiac output.

I Heart Failure with Low Cardiac Output
  A. Degenerative heart disease (arteriosclerotic and hypertensive)
  B. Valvular heart disease (rheumatic, syphilitic, congenital)

II Heart Failure with High Cardiac Output
  A. Cor pulmonale
  B. Congestive heart failure secondary to severe anemia
  C. Beri-beri heart disease
  D. Heart disease in association with thyrotoxicosis
  E. Congestive heart failure secondary to free arteriovenous communications.
    1. Arteriovenous aneurysm
    2. Generalized osteitis deformans
    3. Congenital defects (patent ductus arteriosus)

The high cardiac output occurs in association with diseases in which there is a disproportion between the demands for oxygen and its supply. Thus, in severe anemia or in cor pulmonale secondary to pulmonary disease, the increased output acts as a compensatory mechanism to prevent tissue anoxia due to the low oxygen content of the arterial blood. In thyrotoxicosis it is the increased demand for oxygen which is presumably responsible for the phenomenon in question.

tween partial and complete block. In case of a partial block the drug, by increasing the block, may be instrumental in producing an attack. The improvement from digitalis in other cardiac functions must be weighed against the possibility of this deleterious effect. Such improvement in fact may lessen the frequency of attacks. In addition, not always is the block-producing property of digitalis conducive to development of attacks in the manner above explained. On the contrary, by making the block more permanent, the transition periods from one degree of block to another responsible for Adams-Stokes episodes may be obviated. Digitalis-induced block is rarely associated with Stokes-Adams attacks. In case of complete and permanent A-V block, the occurrence of these attacks cannot be blamed on the transition periods, and digitalis, naturally, cannot have any effect on it. On the other hand, in some cases complicated by partial A-V block the treatment of congestive heart failure with digitalis may result in reduction of the grade of block along with general improvement.[88]

The problem of treatment of cardiac arrhythmias entails a consideration of the etiological factors responsible for their appearance. In instances where they represent a manifestation of an underlying heart disease the attention is primarily directed to the latter condition. The therapy is for the underlying disease and this may incidentally reflect favorably on the arrhythmia. When the abnormal mechanism is known to be of functional origin, existing in the absence of any organic disease of the heart, the arrhythmia *per se* does not necessarily call for treatment. It is only when the state of circulation is envisaged in its entirety that a correct decision can be made regarding the stand one should take in regard to the discovered abnormality of rhythm. Over-treatment must be avoided.

Premature contractions of auricular, nodal, or ventricular origin, when arising on the basis of disturbed physiological processes of a failing myocardium, may promptly disappear with improvement in circulation on exhibition of digitalis. On the other hand it should be remembered that they may indicate digitalis intoxication, if absent prior to digitalization. In that case discontinuance of the drug will lead to their disappearance. These disorders, however, are frequently encountered in people with normal hearts and then hardly warrant the administration of the drug. Rather an attempt should be made to correct the condition (tobacco, caffeinated beverages, alcohol, mental or physical strain) responsible for the disorder. In people who are very conscious of the irregular heart action and are apprehensive because of it, reas-

surance and digitalis may be tried. The drug helps many, but is of no avail in other cases.

Paroxysmal auricular tachycardia is also known to occur quite frequently in the absence of heart disease. It is usually an unimportant and transient disturbance except in patients with low cardiac reserve. In the latter group, when lasting sufficiently long, it can precipitate failure. Mechanical measures (pressure on the eyeballs, massage of the carotid sinus) and drugs, other than digitalis (quinidine, acetyl-B-methylcholine chloride) are customarily employed. Drug therapy is often not productive of the desired effect. If other measures fail, digitalis may be tried. It has been found to be particularly valuable in treatment of this disorder in infancy.[129] The same considerations in large measure apply to tachycardia of nodal origin, which is seen much less frequently than paroxysms of auricular tachycardia. Here again it must be kept in mind that digitalis is known to initiate an attack. On the other hand, the drug may be of value as a prophylactic ration in patients with frequent attacks.

In some patients with auricular tachycardia, neither digitalis alone nor the compression of the carotid sinus alone brings forth the desired result. In such instances, if digitalization is first carried out and then the pressure on the carotid sinus is attempted, conversion to sinus mechanism may take place without any further difficulty.

Ventricular tachycardia is much more serious, as it may culminate in fibrillation of the ventricles with exitus. It is most frequently seen in patients with serious heart disease. Digitalis is not employed; instead quinidine is to be used. Digitalis intoxication may bring on an attack. Adrenalin injected into a vein may also cause it. The bidirectional type of ventricular tachycardia has already been discussed.

Auricular flutter is more commonly found in the presence of heart disease than in its absence. It can be caused by thyrotoxicosis. Digitalis is the drug of choice. Large doses must at times be resorted to in order to produce the desired results. Thirty grains or more may have to be given – three grains three times a day for three days. Not infrequently the flutter is then converted into auricular fibrillation, but with a slower ventricular rate due to the block induced by the drug. With the appearance of fibrillation, the withdrawal of the drug may lead to reversal to normal rhythm. However, such occurrence is far from being the rule and, therefore, cannot be depended upon. It may be a good policy not to stop digitalis administration after conversion into fibrillation, but to continue with the maintenance dose to keep the ventricu-

lar rate down somewhere between 70 and 80 per minute. In obstinate cases, quinidine must be employed. In view of the fact that quinidine decreases the rate of the circus movement with consequent increase in the ventricular rate which may precipitate failure, it is advisable to administer digitalis with the purpose of increasing A-V block prior to exhibition of quinidine.[180]

Like flutter, auricular fibrillation is most common in association with heart disease. Thyrotoxicosis and toxic conditions in general may bring on a paroxysm. In the former instance, thyroidectomy may abolish the arrhythmia. Digitalis frequently gives unsatisfactory results prior to thyroidectomy. Following surgical intervention, if the arrhythmia still persists, quinidine is the drug of choice. Under other circumstances, and particularly in heart failure, digitalis is most highly satisfactory. The marked ventricular slowing on exhibition of the drug has already been commented upon. It takes place in the presence of the perpetuation of the arrhythmia itself. In fact, the auricular rate may increase under the influence of the drug. However, in some instances the drug causes not only ventricular slowing, but also reversal to regular sinus rhythm.[181,182,183] Fibrillation of the auricles may also appear as a result of digitalis intoxication.

The ventricular rate serves as one of the principal guides to the degree of digitalization of patients with auricular fibrillation. It is customary to give enough of the drug to reduce the cardiac rate to between seventy and eighty beats per minute and to maintain it at that level. When this end is achieved with the patient in bed, the same patient may still frequently show an exaggerated response to exercise.[184] To prevent this exaggerated acceleration of the heart it has been advocated to administer the drug in doses sufficiently large to increase the vagal tone and consequently the degree of A-V block.[185] According to Gold[185a] the mechanism is different. When digitalis-induced slowing is by the vagal mechanism (abolished by atropine), exercise may accelerate the rate markedly, but when the slowing is by the extravagal mechanism (not abolished by atropine), exercise rarely accelerates the rate to the same degree. In other words, free physical activity raises the rate to uncomfortable peaks when the mechanism of control is vagal. If larger doses of digitalis are given, the rate control passes to the extravagal mechanism, which prevents the exaggerated acceleration with exercise (see p. 25).

Ventricular fibrillation is a grave disorder and only too frequently leads to a fatal outcome. There is unfortunately no specific therapy. The possibility of this disorder being in some instances the cause of sudden death in digitalized patients has already been mentioned.

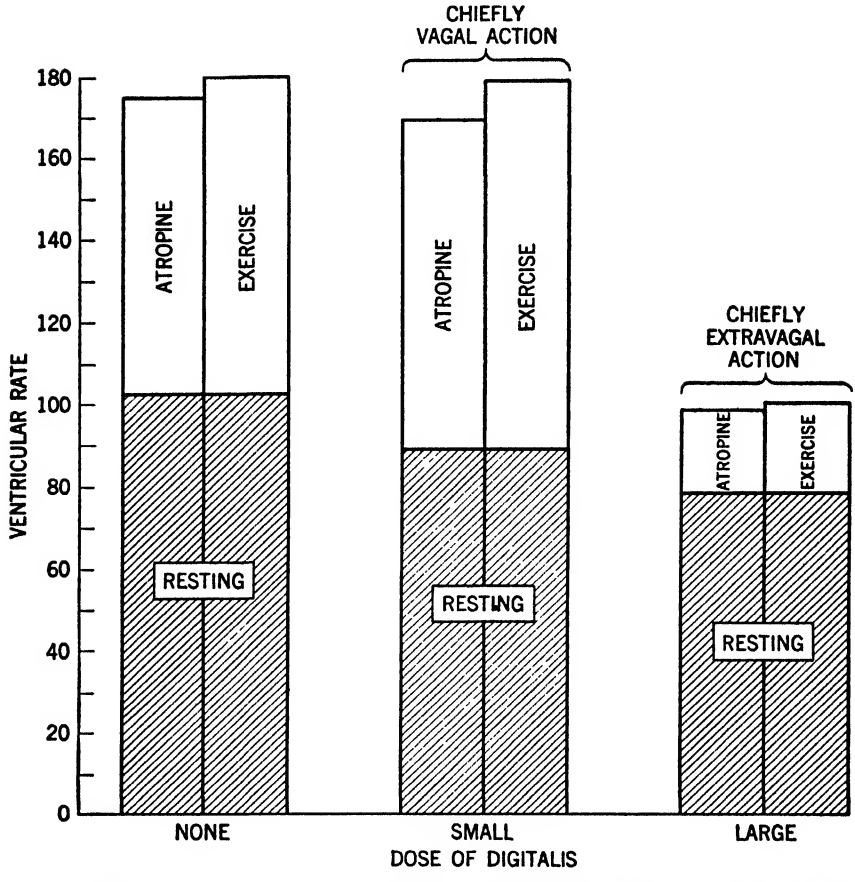


FIG. 7. Effects of exercise and atropine on the heart rate in eleven ambulant patients with heart failure and auricular fibrillation after small and large doses of digitalis. (From H. Gold., *J. A. M. A.*, vol. 132, 1946.)

Conditions other than Those Discussed in which Digitalis is not Indicated

The discussion of digitalis therapy would hardly be complete without mentioning briefly some of the conditions in which the drug is not infrequently employed without clear-cut indications and under circumstances where it cannot be expected to be helpful. This misuse of digitalis is founded on lack of proper understanding of pathological physiology of circulatory failure and misconception in regard to the pharmacological properties of the drug.

The failure of circulation may be of central (cardiac) or peripheral origin. It is only in cases where the heart is at fault that the drug will

be useful. In peripheral circulatory failure, such as seen in shock, attention should be directed to the search for and correction of the factors responsible for the vasomotor collapse. The search is to be conducted not in the heart but elsewhere, as the heart is implicated only secondarily. Still digitalis is given by some physicians to patients in shock because of the fast pulse.

Shock-like manifestations may occur, however, in some patients with congestive failure, particularly when associated with myocardial infarction. In such patients, in addition to the usual signs and symptoms of cardiac failure such as dyspnea, orthopnea, pulmonary congestion, and a large, tender liver, there may also be found the signs of shock similar to those encountered in peripheral circulatory collapse of infection, trauma, or hemorrhage. The peripheral pulses may be feeble, if not altogether absent; the skin may be cold and pale, bespeaking the marked reduction in the peripheral blood flow; the pulse pressure may be low in the presence of a fairly normal diastolic pressure. The pathogenesis of these developments is different from that of peripheral vascular collapse incidental to trauma and hemorrhage. Whereas the latter results from a diminution of the venous return to the heart, in the shock-like picture associated with congestive failure it is the low cardiac output that initiates the morbid processes.[185b] In these circumstances digitalis, along with other measures, may be lifesaving.

The drug is sometimes employed to slow the pulse in a multitude of conditions, such as neurocirculatory asthenia, infections, fever, etc. Digitalis will slow the pulse appreciably only in cases where tachycardia (of sinus origin) is the result of heart disease (failure). Moreover, in some conditions tachycardia represents a compensatory phenomenon, a useful adjustment to altered demands in disease, and treating tachycardia *per se* would be just as unphysiological as concentrating one's attention on energetic measures ' to bring the fever down ' in a febrile illness for which specific therapy may be available.

Routine employment of digitalis in pneumonia of middle-aged or even old people is not warranted, unless there be a co-existing heart disease with failure, or impending decompensation, or when the problem is that of safeguarding patients from the unfavorable effects of the rapid rate in an arrhythmia (auricular fibrillation).[186]

Neither is the use of the drug as a part of routine preoperative care indicated, except in the presence of heart disease, and then only if there is frank decompensation or if there are indications present of impaired

cardiac reserve, or a probability of an impending failure following surgical intervention.

A safe general rule to remember is that in the absence of auricular fibrillation or cardiac enlargement digitalis is rarely indicated. In acute febrile illness, and in post-operative or obstetrical shock, it is of no value.

A point worth emphasis is that once it is decided that digitalis is needed, adequate dosage should be administered, as homeopathic doses so frequently employed are useless.

It is best to give epinephrine cautiously to patients on digitalis therapy. It has been shown that only half of the usual lethal dose of adrenaline is necessary to kill animals receiving non-lethal doses of digitalis.[187] The finding that smaller doses of the drug are needed to produce toxic degenerative changes in the myocardium of dogs receiving adrenalin has already been mentioned.[78] On the other hand atropine appears to have a protective action.[77]

It is believed that calcium administered intravenously produces an almost instantaneous digitalis-like effect on the heart and the result of both drugs given simultaneously is additive.[188] Some investigators believe that this effect must be ascribed to some specific, but unknown, influence of digitalis on the state of the heart, which sensitizes it to calcium.[188a] On the other hand, Friedman and Bine,[188b] in their experiments with the embryonic duck heart, have found that the effects of a digitalis glycoside were not enhanced by excessive amounts of calcium.

Instances of sudden death following intravenous injection of calcium in patients to whom digitalis had been previously administered have been reported.[189] It is best to be cautious in administering calcium to digitalize the patients.

It has been found that desoxycorticosterone acetate does not potentiate the toxic effects of cardio-active principles (digitoxin).[190a] This is interesting in view of the fact that on theoretical grounds such a potentiation might be expected because of the structural resemblance of the adrenal cortical steroids (DCA in particular) to the digitalis glycosides.

Summary and Conclusions

Digitalis is of inestimable value in the therapy of heart disease. Its particular usefulness lies in the treatment of failure.

Although the exact mechanism of production of congestive failure is still a subject for debate, the physiological expression of spontaneous decompensation of the heart may be summed up as follows: (1) A decrease in mechanical efficiency of the heart; (2) Cardiac dilatation; (3) Tendency toward decrease in cardiac output; (4) Rise of venous pressure.

Digitalis has the ability to reverse these tendencies in cardiac decompensation, i.e. it increases the mechanical efficiency of the heart, reduces cardiac dilatation, increases cardiac output, and lowers venous pressure, thereby alleviating the signs and symptoms of decompensation. The increase in efficiency is accomplished without any greater energy expenditure.

There is in addition a limited field of application in treatment of cardiac arrhythmias *per se*.

Administration of adequate but at the same time non-toxic doses of the drug is the keynote of digitalis therapy.

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CHAPTER II

Digitalis Lanata

THE limitations of the bio-assay for digitalis bodies have already been discussed. Preparations of the same potency with regard to their ability to produce lethal effects in animals used for biologic standardization may vary in their therapeutic potency as applied to clinical practice. Examples of these discrepancies have been reported by a number of investigators in the case of many different products, including the purified glycosides of digitalis, such as digitoxin (digitalin Nativelle),[1] gitalin (verodigen),[2] and others. DeGraff and collaborators[3] remark on the confusion resulting from the marked difference among various digitalis principles. They point out the fact that without extensive clinical experience the physician encounters great difficulties in maintaining the same level of therapeutic effectiveness when one preparation is substituted for another.

These considerations make welcome the introduction of a digitalis body which can be standardized by weight and which would contain a constant amount of a glycoside or some fixed proportion of several glycosides. Reliance could be placed on such a product to produce the same therapeutic effect, within the limits of biologic variations, irrespective of the particular sample dispensed. Preparations of Digitalis lanata (digilanid) meet these requirements as they possess the desired qualifications of constant composition and potency.

SOURCE AND CHEMICAL STRUCTURE

Digitalis lanata is indigenous to the Balkans. Efforts are being made to grow this species of digitalis in the United States, but so far have

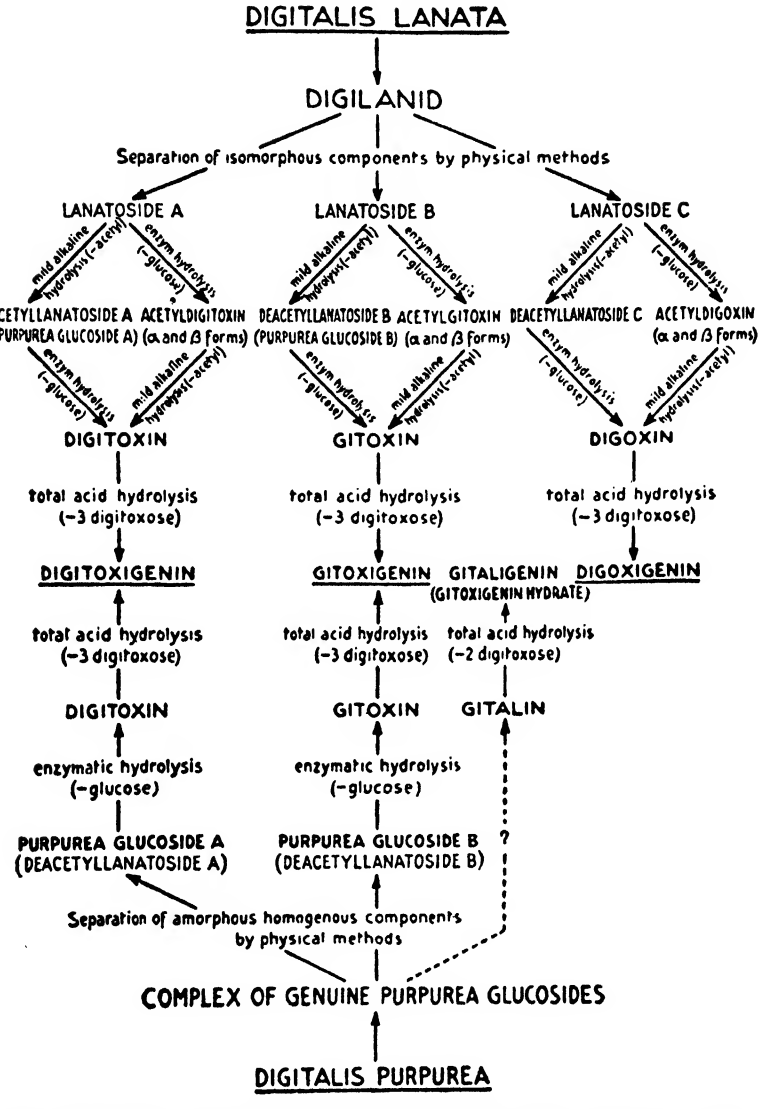
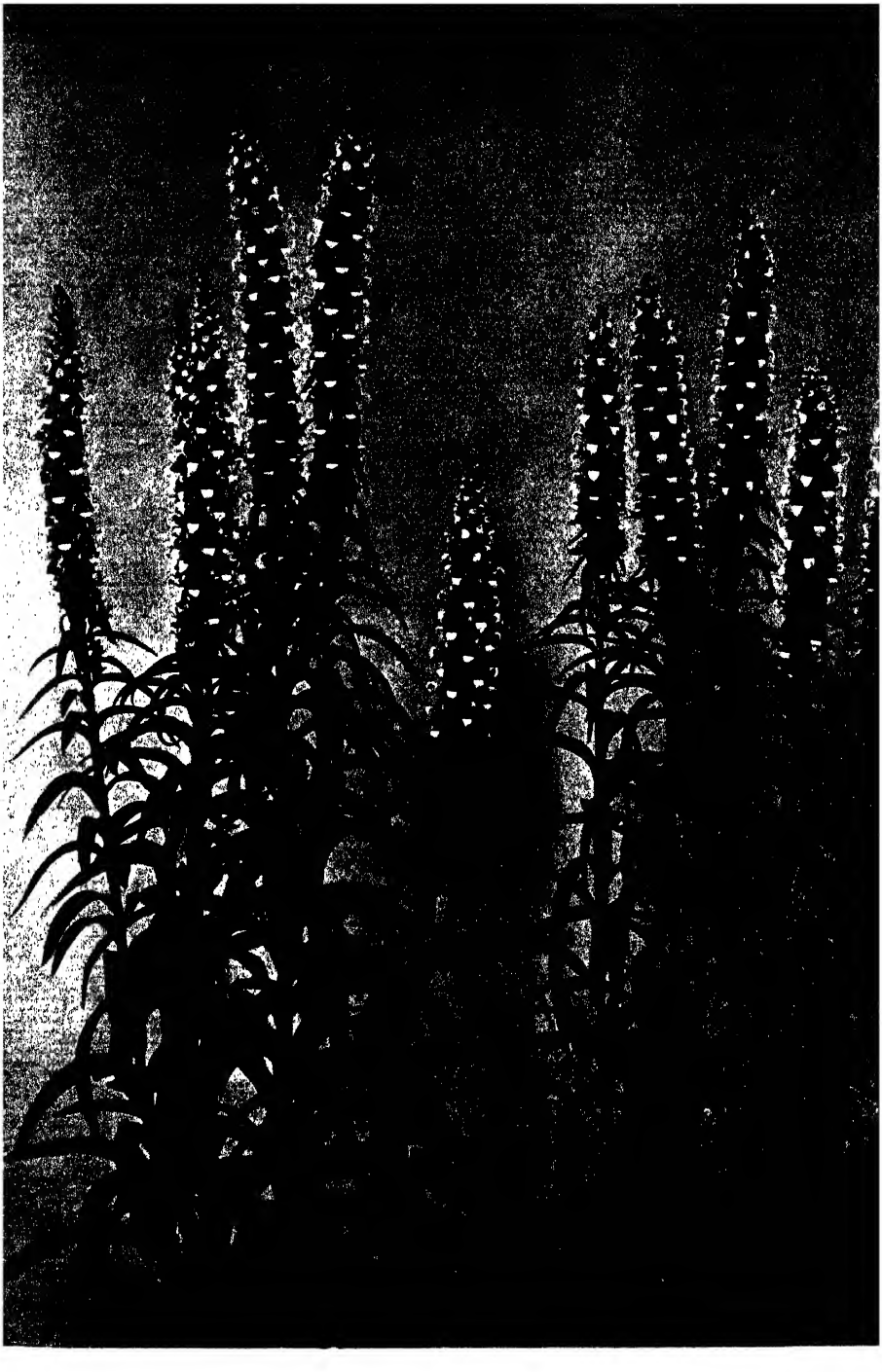


FIG. 8. Interrelationship of the Lanata and Purpurea glycosides. (From A. Stoll, *The Cardiac Glycosides*, Pharmaceutical Press, London, 1937.)

not been too successful. If it is eventually grown in this country in sufficient quantities the question arises whether or not the plant will be rich enough in cardiac glycosides as compared with Digitalis lanata cultivated in Europe.

Credit for the isolation of the pure, active principles of Digitalis lanata must be given to Stoll and Kreis. The results of their chemical

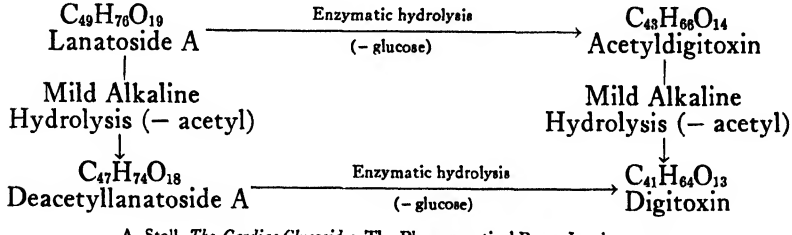


DIGITALIS LANATA

investigations have necessitated a revision of the heretofore prevailing views with regard to cardiac glycosides. Their research has shed a new light on the subject of the chemistry of active cardiac principles.

Stoll[4] was able to isolate from the leaves of Digitalis lanata three chemically pure substances known as lanatoside A, lanatoside B and lanatoside C respectively. They all contain an acetyl group which on mild alkaline hydrolysis can be split off from the original moiety, giving rise to deacetyllanatosides A, B, and C. Further research by Stoll demonstrated the presence in the leaves of the plant of an enzyme, lanatosidase, capable of splitting from lanatosides the glucose which is attached at the end of the chains of sugars. As a result of such cleavage the acetyl glycosides are obtained. These, on alkaline hydrolysis, also loose the acetyl group, yielding the corresponding glycosides. These glycosides are: digitoxin from lanatoside A, gitoxin from lanatoside B, and digoxin from lanatoside C. The table below illustrates the conversion involved in the case of lanatoside A:

TABLE I



A. Stoll, *The Cardiac Glycosides*, The Pharmaceutical Press, London, 1937.

On alkaline and enzymatic hydrolysis of the lanatosides, both the glucose molecule and the acetyl group are removed and the respective glycosides are liberated. Stoll has also demonstrated the identity of the two out of three glycosides thus obtained from Digitalis lanata with those found in Digitalis purpurea. Thus digitoxin of Digitalis purpurea is identical with the glycoside representing the product of hydrolytic cleavage of lanatoside A of Digitalis lanata, while gitoxin of the ordinary digitalis corresponds to the derivative of lanatoside B of Digitalis lanata. Digitoxin from both sources on further acid hydrolysis yields three molecules of the same sugar (digitoxose) and the aglucone digitoxigenin (the cardio-active principle). Similarly gitoxin from both plants on acid hydrolysis yields the three molecules of digitoxose and the aglucone gitoxigenin. At the same time, however, no counterpart of the glycoside digoxin, obtained from lanatoside C, can be found in

the ordinary digitalis. On the other hand the latter contains one glycoside (gitalin) not found in lanata.

Thus Stoll has succeeded in demonstrating that the glycosides digitoxin and gitoxin, for a long time known as pure, active principles of Digitalis purpurea, are actually degradation products of the compounds as they exist in the natural state. These natural glycosides in the ordinary digitalis are identical with those in Digitalis lanata (lanatosides) with only one exception: They lack the acetyl group and are, therefore, known as deacetyllanatosides A and B (yielding with the loss of glucose on hydrolysis the glycosides digitoxin and gitoxin respectively). The natural glycosides for gitalin in Digitalis purpurea has not yet been isolated.

TABLE II

	Natural Glycoside		*Glycoside*	*Sugar*	*Aglucone*
Leaves of Digitalis Purpurea	Deacetyllanatoside A	(− glucose)	— Digitoxin	(−)3 Digitoxose	— Digitoxigenin
	Deacetyllanatoside B	(− glucose)	— Gitoxin	(−)3 Digitoxose	— Gitoxigenin
Leaves of Digitalis Lanata	Lanatoside A	− {glucose and Acetyl}	— Digitoxin	(−)3 Digitoxose	— Digitoxigenin
	Lanatoside B	− {glucose and Acetyl}	— Gitoxin	(−)3 Digitoxose	— Gitoxigenin
	Lanatoside C	− {glucose and Acetyl}	— Digoxin	(−)3 Digitoxose	— Digoxigenin

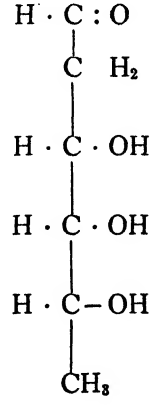
The interrelationships between the two species of digitalis plant can be seen at a glance from the diagram reproduced from the paper by Stoll.

Thus it has been shown conclusively that the glycosides digitoxin, gitoxin, digoxin (and also possibly gitalin) are the products of degradation of the natural glycosides which have lost carbohydrates (glucose) during the process of purification. The significance of the sugars in reference to cardiac activity has been investigated by Rothlin[7] and others. Rothlin has demonstrated in the course of comparative pharmacological experiments on animals that the effect decreases in direct proportion to the decomposition of the original glycoside down to the aglucone. On the basis of these findings Weese concluded that 'the natural glycosides present in the plant are far more effective than any artificial preparations hitherto produced by decomposition.' Owing to the protective process of extraction devised by Stoll, the active prin-

ciples of Digitalis lanata can be isolated in their initial form without degradation.

Thus the glycosides are more active than their corresponding aglucones because of the sugar contained in their moiety (the sugar being digitoxose in the case of principles derived from digitalis). However, it is believed by some investigators that due to an inherent difference between glucose and the desoxy sugars (digitoxose) the former does not have the same influence on activity of cardiac principles as the latter.[8] In other words, the addition of a molecule of glucose to the glycoside does not have an effect equivalent to that obtained by addition of digitoxose to the aglucone.

The rather unusual pentose sugar (digitoxose) found in conjugation with the aglucone in the glycoside moiety is found in nature only in digitalis bodies. The structural formula appears below.

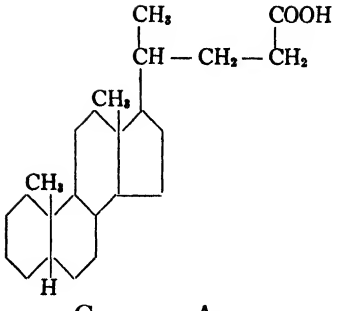


Digitoxose

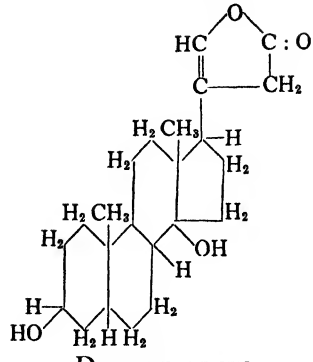
The complex structure of the aglucones was poorly understood until their chemical relation to the acids and sterols in general had been discovered. It will be recalled that the basic structure is a cyclopentenophenanthrene nucleus to which is attached a lactone ring. In addition certain groups are attached in specific positions varying with the particular aglucone.

Smith[5] who described digoxin found it to be isomeric with gitoxin. Digoxigenin, the aglucone of digoxin, is also isomeric with gitoxigenin, the aglucone of gitoxin.

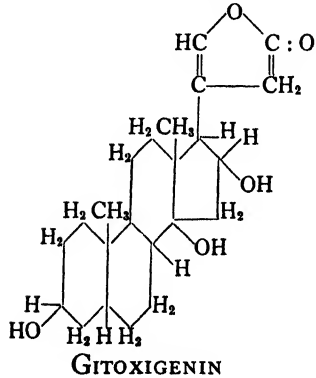
The glycoside content of Digitalis purpurea is appreciably smaller as compared with Digitalis lanata. The former possesses only a fraction



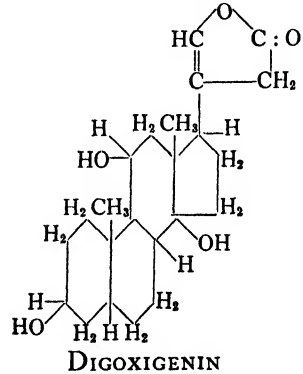
CHOLALIC ACID



DIGITOXIGENIN



GITOXIGENIN



DIGOXIGENIN

of the activity of the latter.[4,6] The yield of pure genuine glycosides from Digitalis purpurea is very much smaller than that from Digitalis lanata, probably on account of their amorphous character and the presence of large quantities of interfering substances.[4] Stoll states that the isolation of the genuine (natural) cardiac glycosides of Digitalis purpurea is, therefore, more difficult and has so far only a scientific interest. He feels that lanata should be preferred to purpurea for the technical manufacture of crystalline pure products on account of its considerably greater glycoside content. Moreover, the additional presence of component lanatoside C, lacking in Digitalis purpurea, provides a completion of the therapeutic activity. It is obvious, however, that the great services rendered for so many years by ordinary digitalis remain unimpaired. Digitalis purpurea has been an indispensable part of the therapeutic armamentarium. Its use led to a study of other digitalis species and derivatives which possess certain advantages discussed in this text.

Although the components of both kinds of digitalis plant vary in

different specimens within one and the same species, they do so considerably less in the case of lanata. The proportions of lanatoside A to lanatoside C from different localities can be seen in the following table.

TABLE III

(Dr. W. Kreis)

No.	*Origin*	*Content of Lanatoside A in Per cent*	*Content of Lanatoside C in Per cent*	*Proportions of Lanatoside A to Lanatoside C*
1	Neighborhood of Vienna	48	37	1 : 0.77
2		48	36	1 : 0.75
3		47	37	1 : 0.79
4		45	37	1 : 0.82
5		49	36	1 : 0.74
6	Neighborhood of Basel	55	39	1 : 0.71
7	Neighborhood of Vienna	46	42	1 : 0.92
8		34	52	1 : 1.53
9	From France	25	62	1 : 2.48
10		26	66	1 : 2.54

For comparison, the proportion of glycosides (digitoxin and gitoxin) in Digitalis purpurea from different localities is represented in the following table.

TABLE IV

(Dr. W. Kreis) 1925–39

		Extract of 1 kg. of Dried Leaf		
No.	*Origin*	*Digitoxin Fraction*	*Gitoxin Fraction*	*Proportion of Digitoxin to Gitoxin*
1	Thuringia	0.005 g	0.42 g	0.012
2	Black Forest	0.50 g	0.20 g	2.5
3	Vauges	0.63 g	0.0 g	63.0
4	Swiss Jura (cultivated)	0.15 g	0.70 g	0.21
5	Vauges	0.49 g	0.05 g	9.8
6	Harz	0.13 g	0.26 g	0.5
7	Unknown Commercial	0.27 g	0.13 g	2.1
8	Unknown Commercial	0.18 g	0.54 g	0.33
9	U.S.A. (Cultivated)	0.33 g	0.29 g	1.14
10	Unknown Commercial	0.21 g	0.70 g	0.30

The table shows marked variations in the composition of Digitalis purpurea leaves. For example, while the plant from Thuringia has practically no digitoxin but is rich in gitoxin, the specimen from Vauges is rich in the former principle but contains none of the latter.

Even the slight variations in the isomorphous crystallized mixture extracted from Digitalis lanata are corrected in the preparation of digilanid containing all the three pure glycosides. Due to precise analytical study of each of the three lanatosides (A, B, and C), it has been possible to find a quantitative method of analysis for determining the proportions of the three components in the total final product. Thus the digilanid mixture introduced into clinical practice has been found to contain about 46 per cent of lanatoside A, 17 per cent of lanatoside B, and 37 per cent of lanatoside C.

It is considered[4] that by reason of their large molecular size these lanatosides may be the most active cardiac glycosides isolated from digitalis. The assumption that the total glycoside preparation of digilanid containing all three lanatosides adequately replaces the whole leaf has been confirmed by clinical experience.

Pharmacology

Extensive pharmacological studies of lanatosides have been carried out by Rothlin.[9]

Rothlin found that the toxicity of digilanid in a cat of 0.34 mg. per kg. and in a frog of 620 F.D. per mg. was according to the order of magnitude of digitoxin. It is considerably lower than for the glycosides of the strophanthus or scilla groups.

In the course of studies by Rothlin the results of forty-two tests showed that after oral ingestion the arrest of cardiac action required about twice the amount of glycoside than after intravenous injection. In comparison with other glycosides he considered this proportion to be very favorable, indicating good absorption from the gastrointestinal tract. By subcutaneous injection the toxic dose for the cat was found to be 0.35 mg. per kg., thus being practically identical with the intravenous dose. The glycoside effect, however, was delayed because of slow absorption and the animals succumbed only after twenty-four to forty-eight hours.

As it is known that organs other than the heart also absorb cardiac glycosides, Rothlin set out to determine the consumption dose with an intravenous injection for the whole animal and the eviscerated animal. In addition, determinations were made on heart-lung preparations. Ex-

TABLE V

(E. ROTHLIN)

TOXICITY OF DIGITALIS GLYCOSIDES

Glycoside	*Frog (Medium Lethal Dose, Sub-cut. inj., Timeless Method) Frog Unit per mg.*	*Cat (Intravenous Infusion According to Hatcher) Cat Unit = mg. per kg.*
Digilanid (total complex)	620	0.343
Lanatoside A	690	0.380
Lanatoside B	540	0.400
Lanatoside C	640	0.281
Deacetyllanatoside A	690	0.368
Deacetyllanatoside B	315	0.369
Digitalin Cryst.	400	0.420
Digoxin	650	0.280
K-Strophanthosid	1850	0.126
Cymarin	1500	0.146
Ouabain (g-Strophanthin)	2400	0.100
Scillaren A	1200	0.145

periments on the eviscerated animal whose organs below the diaphragm were entirely removed consumed only 70 per cent of the total consumption dose, which is chiefly distributed among the heart, muscles, and skin. Thus, apparently only 30 per cent is taken up by the abdominal organs. In experiments on heart-lung preparations it was discovered that 1 kg. of heart consumes twenty-seven times more glycoside than 1 kg. of the whole animal and a little over nine times more than 1 kg. of abdominal viscera, thus demonstrating the selective fixation of digilanid, by the tissues of the heart.*

With the isolated heart of the frog, the heart of the cat *in situ*, and the heart-lung preparations, all three lanatosides were shown to exert the familiar effects of cardio-active drugs: A period of latency, increased force of contraction, and finally a cardiac standstill. With the artificial perfusion of the heart of a frog *in situ*, the cardiotonic effects were well demonstrated on using concentrations of only 1:1,000,000 or 1:2,000,000 of digilanid.

The studies on cumulation were carried out with the Hatcher-Eggleston technique. The animal is given a preliminary dose of 50 to 80 per cent of the lethal dose. After a certain interval of time the com-

* Some investigators believe that selective absorption by the heart out of proportion to its weight, as compared with other organs, does not exist.

plement dose for inducing cardiac arrest is determined. Comparative studies were done by this method with digilanid, strophanthin, and digitoxin showing relatively marked cumulation for digilanid.

Also comparative studies were done with several preparations of digilanid complex from different sources and different seasons. The medium lethal dose was found to be fixed at 0.343 mg. per kg. with maximal deviations from the medium being well within the limits of error of the method of biological titration. These results confirmed a very satisfactory constancy of composition. Rothlin also found the test for stability to yield good results. Control solutions kept at room temperature yielded the same strength during the course of two years.

The stability was also tested by Vos.[10] A liquid preparation of digilanid was opened, recorked, and kept in a bathroom medicine cabinet for about four years. When compared with a fresh preparation no significant deterioration, as determined by cat assay, was found.

Reports of clinical investigations bear testimony to the good absorbability, rapid action, and effectiveness of digilanid. Herrmann[11] finds that the drug is rapidly absorbed and acts promptly. He cites persistence of effect as another advantage in favor of the preparation. Sieve[12] states that the drug is well absorbed from the gastro-intestinal tract and is well tolerated. The author presents a clinical comparison of patients treated with ordinary digitalis and digilanid. The patients treated with digilanid manifested better tolerance for it than for the powdered leaf of purpurea, as shown by a greater freedom from nausea, vomiting, and disturbances of rhythm. Sieve concludes that ' chemically pure digitalis glycosidal products are more satisfactory for clinical use than crude drug preparations.' Scherf and Boyd came to the conclusion that digilanid ' represents a highly active, powerfully cumulative form of digitalis which exhibits all of the properties expected from a good preparation of this drug.' Christian[13] states that therapeutically digilanid appears to have the advantages over most of the Digitalis purpurea preparations ' of being crystalline pure, well and quickly absorbed from the gastro-intestinal tract, non-irritating to stomach and muscles and stable.' He adds that whether or not it is superior to digitoxin, which possesses the same toxicity as digilanid as tested on cats and dogs, still is unproved.

The reports of European clinicians carry the same favorable note. Thus Staehelin[14] feels that Digitalis lanata acts somewhat more rapidly but is less cumulative than Digitalis purpurea. He states that it is ' better tolerated by the gastro-intestinal tract than other digitalis prep-

arations possessing similar action. In principle, Digitalis lanata, can be used in cases where Digitalis purpurea is likely to be indicated. Moreover, Digitalis lanata may also be used in cases in which Digitalis purpurea causes gastric disturbances, especially vomiting.' Oettel[15] finds the preparation very useful, readily absorbed, and well tolerated.

Standardization and Preparations

The chemical purity of digilanid makes possible standardization by the gravimetric method. The chemical assay assures constant potency. As a result, preparations of digilanid can be expected to have a

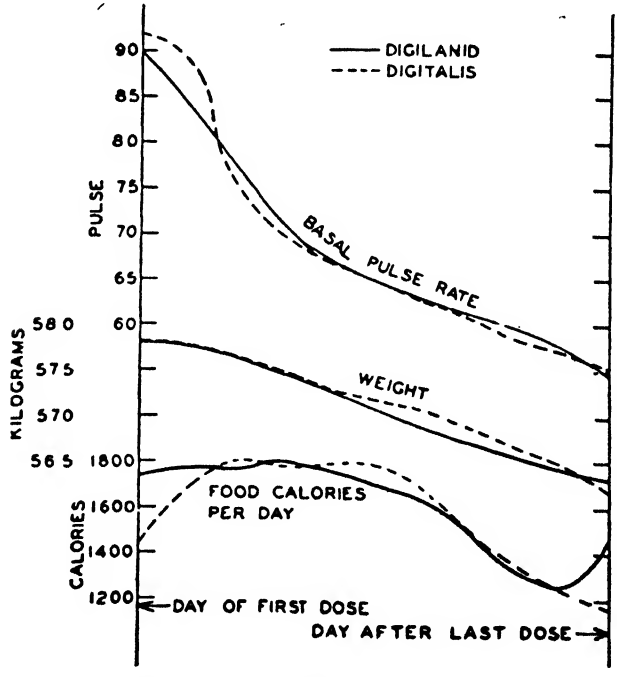


FIG. 9. Mean curves of basal pulse rate, weight, and caloric intake during digitalization with digilanid orally (six digitalizations) and digitalis leaf (three digitalizations). In constructing these mean curves the time scales of the individual curves were varied so that the horizontal lengths of the curves were equal regardless of the actual time required for digitalization. (From W. A. Adams and L. Gregg, *Am. Heart J.*, vol. 19, 1940.)

constant therapeutic effect proportionate to size by weight, within the limits of biologic variations of individual requirements for and tolerance of the product.

By van Wyngaarden modification of the Hatcher-Brody technique, 0.33 mg. of digilanid is equivalent to one cat unit.[9] Compared

with Digitalis purpurea, the clinical equivalents of 0.1 gm. (1.5 grains) of whole leaf digitalis are represented by 30 drops of the liquid preparation or approximately one tablet (0.33 mg.) of digilanid.

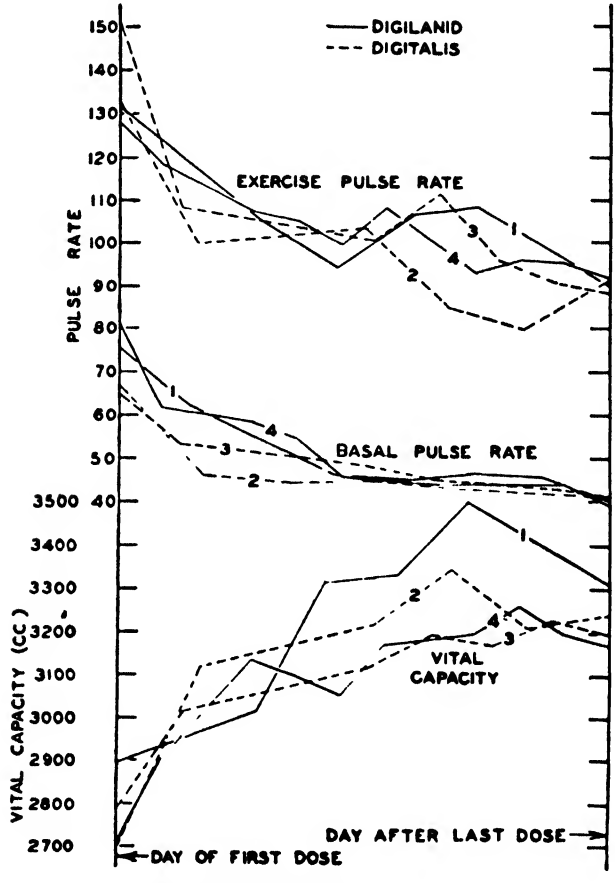


FIG. 10. Curves of pulse rate and vital capacity during digitalization with digilanid and digitalis leaf orally. The 'exercise pulse rate' was counted for one minute, beginning fifteen seconds after exercise. The time scales of these curves are adjusted in the same way as those of Fig. 2. The numbers on the lines indicate the order of the digitalizations. Lines with the same number correspond. (From W. A. Adams and L. Gregg, *Am. Heart J.*, vol. 19, 1940.)

There are preparations available in solid and liquid form. For oral use digilanid is dispensed in tablets (⅓ mg. per tablet) and as a liquid (⅓ mg. per 1 cc.). There are also ampules available containing 0.2 mg. per cc. For rectal administration suppositories can be used and they contain 0.5 mg. of digilanid. Bauke suggests a microclyster for rectal use when suppositories are not available. The microclyster consists of

3 to 5 cc. of 10 per cent glucose solution mixed with 25 to 30 drops of digilanid solution and 3 to 5 drops of tincture of opium.

Clinical Applications

Adams and Gregg,[16] acting on the assumption that the therapeutic efficiency of a new preparation 'must equal or exceed that of standard preparations before it can be accepted for use . . . in spite of any advantages of accurate dosage, uniformity, and stability which it may possess,' undertook to make a clinical comparison of digilanid and the powdered leaf of digitalis. Two patients were repeatedly digitalized with digilanid and a standard preparation of digitalis leaf. A greater number of patients were digitalized, and some of them were kept on digilanid. A third group was changed from a maintenance dose of digitalis leaf to a maintenance dose of digilanid. The unit dose of digitalis leaf was 0.1 gm. (U.S.P. XI); the unit dose of digilanid was ⅓ mg.

For controlled comparisons of digilanid and digitalis leaf two patients were repeatedly digitalized in the hospital in accordance with a constant dosage pattern, until a definite end point had been reached in each case. To show any difference that might exist between the two preparations in toxic as well as therapeutic effect, mild intoxication was produced. The caloric, fluid, and salt intake were at all times kept at a constant level. Both patients had been followed for several years previous to this study and were known to have a low, but more or less constant, cardiac reserve. One patient, a woman, had rheumatic heart disease and auricular fibrillation. To compare digitalis preparations, she was given six units of one of them on one day, and two units twice a day thereafter, until the heart rate under basal conditions was 55 per minute. After an interval of four weeks without any medication, the same procedure was carried out with the other preparation. The cycle was repeated a number of times with each drug. The average dose of digitalis leaf was twenty-nine units (2.9 gm.), of digilanid orally, twenty-eight units (9 mg.), and of digilanid intravenously eighteen units (6 mg.). The observations, including the evaluation of change in various symptoms and signs such as loss of weight, fluid balance, circulation time, venous pressure and subjective improvement, failed to give evidence of difference in effect between the two preparations (when they were given orally). The other patient also had rheumatic heart disease and auricular fibrillation. In his case six units of either drug were given on the first day and one unit daily thereafter until the basal pulse rate reached 40 per minute. In addition to the ob-

servations made on the first patient, the effect of standardized exercise was observed. The average requirement of powdered leaf was twelve units (1.2 gm.), and of digilanid fourteen units (4.7 mg.). In addition to subjective evidence of increased exercise tolerance, the control of the heart rate response to exertion and the increased vital capacity all indicated that digitalis bodies were similarly beneficial. None of the other observations, including evidence of mild intoxication, showed any difference in action between the two drugs.

In the other group of twenty-nine patients with degenerative, hypertensive, rheumatic, and syphilitic heart disease, with both normal rhythm and auricular fibrillation, digitalized in the hospital and in the out-patient department, the effect of digilanid seemed indistinguishable from that which would have been expected from the leaf.

The third group of twenty-three patients received maintenance doses of digilanid for various periods in the hospital and out-patient department. Ten of these were digitalized with digilanid. The maintenance dose varied from 1 to 5 grains a week (⅓ grain daily in six out of ten cases). Thirteen patients were changed from maintenance with the powdered leaf to maintenance with digilanid. All of the thirteen patients were changed from digitalis to an equal unit dose of digilanid without evidence of any difference in the effect of the two preparations. In one patient who was nauseated immediately after taking each dose of powdered digitalis leaf, and in another patient who had very minor abdominal discomfort with belching on taking digitalis, the change to digilanid abolished these symptoms.

Thus the similarity of digilanid and the powdered leaf used unit for unit under clinical conditions was found to be quite striking, with only minor variations. The same wide individual variation in dose that is common with powdered leaf was also observed with digilanid. The authors felt that the effectiveness of digilanid was the same as that of the powdered leaf throughout the series. Neither was there any significant difference between the two preparations with respect to the relation of the therapeutic dose to the dose giving rise to symptoms or signs of intoxication. In the two cases in which the ordinary digitalis produced gastro-intestinal symptoms which disappeared after the medication had been changed to digilanid, there was probably local irritation without true intoxication. The authors concluded that ' digilanid is a potent digitalis preparation, equal in clinical effectiveness to a standard preparation of the powdered leaf.'

Batterman, Holman, and DeGraff[8] made their studies on twenty-

three patients exhibiting some degree of congestive failure with normal rhythm and auricular fibrillation. Hypertension, coronary sclerosis, rheumatism, and syphilis were the etiological factors of heart failure in this group. None of the patients received any digitalis preparation three weeks prior to this study. Digitalization was accomplished by oral administration. Following a preliminary control period of absolute bed rest, oxygen (if necessary), sedation, limited fluids, and dietary restrictions, the patients were digitalized rapidly with digilanid orally by one of two plans. Eighteen patients received within the first

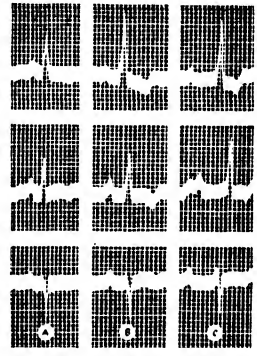


FIG. 11. Alterations in electrocardiographic complexes produced by digitalization with digilanid orally in a patient with hypertensive heart disease. A. Control. B. After 24 cat units (7.92 mg.) in twenty-four hours. C. Forty-eight hours after digiltalization. (From R. C. Batterman, D. V. Holman, and A. C. DeGraff, *Ann. Int. Med.*, vol. 14, 1941.)

twenty-four hours approximately 0.1 cat unit (0.033 mg.) of the drug per pound of body weight. These patients were thereafter given large single daily doses equivalent to one-half this amount until minor toxic symptoms were evident. The second plan for the remaining five patients consisted of single daily doses of approximately 0.05 cat unit per pound of body weight until toxic effects were apparent. All patients had repeated electrocardiograms, were weighed daily and generally observed closely for evidences of improvement, changes in blood pressure, ventricular and pulse rates, and signs and symptoms of toxicity. In seven patients, in fifteen to twenty days following the discontinuance of therapy with digilanid, Digitalis purpurea was given according to the dosage plan identical with that of the previously administered course of digilanid. In addition to the group of twenty-three patients observed, as described above, in the hospital, twenty ambulatory patients with chronic auricular fibrillation were studied with regard to the suitability of digilanid for maintenance dosage. The maintenance requirements with Digitalis purpurea for these patients

was fairly well established and they were known to be rarely asymptomatic unless their digitalis was discontinued or decreased. On the basis of the cat-unit potency, digilanid was substituted for digitalis in identical doses.

In eighteen hospital patients treated in accordance with the first plan of rapid digitalization, satisfactory therapeutic response was obtained within one to two days with a dose ranging from 3.3 to 8.9 mg. (average 6.6 mg.). In three patients the therapeutic and toxic doses were identical, not an uncommon occurrence with the rapid method of digitalization. The toxic dose for the entire group ranged between 4.3 and 16.8 mg. Of the five patients digitalized according to the second plan, the therapeutic and toxic doses were within the range found in the case of rapid digitalization in the first group. This is contrary to the general experience with regard to the difference in total dosage required by the two methods of administration. It may be explained by the very small number of patients studied in the second group, which limits the significance of a statistical analysis.

In the group of seven patients in whom the comparative potency of digilanid and the ordinary digitalis was studied, in spite of the impossibility of achieving exactly identical conditions, four patients required approximately the same amount of the glycoside and Digitalis purpurea (in terms of cat units). In two patients digilanid was more potent than the leaf, while in the remaining patient the relationship was reversed. Maintenance with digilanid was achieved without difficulty and in the same dose substituted for the digitalis leaf. There was no objective evidence for superiority of one preparation over the other. Characteristic changes in the electrocardiograms were produced by digilanid in doses comparable to those of ordinary digitalis. No difficulties were encountered with regard to the administration of digilanid. No gastro-intestinal irritation was observed in any of the forty-three patients studied. This is contrary to what may be expected with any cardio-active drug taken by mouth, and constitutes the advantage of digilanid over digitalis leaf, provided this is confirmed by further studies in large groups of patients. The authors state that ' the mixture of pure crystalline glycosides combined in constant proportions satisfied with a high degree of perfection the criteria for a satisfactory digitalis preparation. . . . If the gravimetric method of assay permits greater accuracy and uniformity of dosage regardless of the sample dispensed, then digilanid would possess definite advantages over the powdered leaf of Digitalis purpurea.'

The authors concluded that digilanid in its effectiveness and clinical potency, cat unit for cat unit, appears to be identical with powdered digitalis leaf and that the ratio of toxic to therapeutic dose also coincides with general experience in the use of ordinary digitalis. They felt that elimination and, therefore, cumulation of digilanid must be within the range allowing slow digitalization and maintenance of a desired therapeutic effect.

Laplace[16] presents a clinical evaluation of potency of digitalis U.S.P. X, U.S.P. XI, and digilanid, in terms of the ability of these preparations to slow the ventricular rate in cases of auricular fibrillation. Observations were made on seventeen patients with degenerative, hypertensive, and rheumatic heart disease. The method consisted of digitalizing each patient with one of the three preparations studied and thereafter giving a constant daily dose which was the same for all patients irrespective of individual therapeutic indications. The daily dose of digitalis U.S.P. X was 1.5 grains, of digitalis U.S.P. XI 1 grain, and of digilanid 1/200 grain (⅓ mg.). With ventricular rate as the only objective criterion for comparing the action of the three drugs, the author found that at rest the effect was the same with ⅓ mg. of digilanid as it was for 1.5 grains of digitalis U.S.P. X or 1 grain of digitalis U.S.P. XI. However, the dose of digilanid of only ⅓ mg. was found to be slightly less effective than the ordinary digitalis in doses above mentioned in controlling the ventricular rate during exercise. As the acceleration of the rate during exercise is stated to be due in the average case to decreased vagal tone,[18] this difference may be interpreted to signify that the slight variation in potency between digilanid and digitalis may involve only vagal action. Four patients stated that they preferred digilanid to digitalis because it was ' easier to take ' or ' less nauseating.'

Rimmerman[19] has treated with digilanid twenty-seven patients in congestive failure with regular rhythm and auricular fibrillation. The daily observations on all patients included the estimation of fluid intake, urinary output, weight, arterial pressure, cardiac rate, and pulse, along with the estimate of the general condition and the state of failure. In addition, electrocardiograms and two-meter x-ray films of the chest were done in all cases. The patients were divided into two groups. In one group, comprising nine patients, it was felt that the condition was urgent enough to require rapid digitalization by intravenous route. In the other group of eighteen patients, the slow digitalization method was employed. The author found 4 cc. given intravenously to be the optimum dose while with 2 cc. the effect was neither as prompt nor

well sustained. On the other hand, it was felt that 8 cc. constituted a definitely excessive dose which might lead to the development of toxicity. Following the intravenous administration of 4 cc. of digilanid, the drug was also given orally, as soon as possible, in the dosage of one tablet three times daily. Additional intravenous digilanid was given only when indicated. In only one instance out of nine was it necessary to administer the supplementary dose in order to obtain a prompt and satisfactory result. The most rapid and dramatic response was observed in cases with auricular fibrillation. In one patient the pulse rate dropped from 190 to 108 within three hours. In most instances the major effect was accomplished within four hours, and in some within only two hours. All patients in the first group responded well, with relief of symptoms and signs of failure. In the group treated orally, all eighteen patients showed more or less clinical improvement within an average of four days. This improvement was manifested by slowing of the pulse rate, disappearance of pulse deficit, increased urinary output, loss of weight, disappearance of edema, disappearance or decrease of orthopnea and dyspnea. Digitalization as shown by the slowing of the ventricular rate occurred on an average in thirteen days, the shortest time being four days and the longest twenty-two days. The slow method of digitalization in this group consisted of the administration of one tablet of digilanid three times daily. The average oral digitalizing dose was found to be 12⅔ mg. (38 tablets), and the maintenance dose ⅓ mg. (1 tablet) in all but one patient who required ⅔ mg. (2 tablets) for the maintenance of full effect. It was noted that in this group of cases there seemed to be no relation between the dose of the drug necessary for complete digitalization and the weight of the patient or the amount of edema. All patients were kept at absolute bed rest until there was definite improvement. In only four of the eighteen patients did symptoms of overdigitalization appear. These consisted of nausea, vomiting, and electrocardiographic evidence of toxic effect. The group included a few patients with thyrotoxicosis. In these, the cardiac slowing was either insignificant or not as marked as in the other types of heart disease. However, the loss of edema and other signs of improvement were equally noticeable. Patients with hyperthyroidism required two to three times the amount of digilanid for a maintenance dose as did the non-hyperthyroid patients. Thus, while the digitalization alone is not sufficient for the treatment of a thyrotoxic heart, it may be a worthwhile adjunct to the general management of thyrotoxicosis complicated by congestive failure.

Kruskemper and Hurthle[20] treated with digilanid seventy-nine patients in cardiac decompensation with degenerative types of heart disease and valvular heart disease (rheumatic, syphilitic). Treatment was usually started with 1 mg. dose daily for the first three days, followed by daily doses of 0.75 mg. This they found to be sufficient for re-establishing compensation within six to eight days without producing any untoward symptoms. Belz[21] found digilanid to be a satisfactory preparation for post-operative treatment of patients in whom there were indications for digitalization following surgical operations. Roth[22] found five or six drops of liquid preparation to be an adequate maintenance dose in many patients. There are many other reports in foreign literature attesting to the efficacy of the drug.

Basing his practice on the knowledge of the essential role played by the calcium ion in the normal functioning of the heart and some similarities of action on the heart by calcium and digitalis bodies, Klatschko[23] used calcium (bromolactobionate) in conjunction with digilanid and reported 'a better and more rapid action.' This practice of combined therapy is not in use in this country. Its rationale is rather difficult to understand even in view of the possible dependence of the activity of digitalis bodies on the calcium concentration of the blood (Loewy and Rothlin). Administration of calcium intravenously to digitalized patients has been fatal in several instances.

Rectal administration of digilanid in the form of suppositories was employed by Diasio[24] with success in treatment of congestive failure in six patients. The author felt that the limited bulk of the suppositories and their non-irritating nature, in addition to fixed constant composition, overcame the objections heretofore applicable to rectal therapy with digitalis. Similar favorable reports have been made by others. This route is used but very seldom, however. When the drug cannot be given by mouth, it is usually injected into a vein.

Summary and Conclusions

Digilanid is a preparation of Digitalis lanata, of constant composition in contrast to official digitalis. It represents a mixture of pure natural glycosides of the lanata leaf and can be standardized gravimetrically. In this regard digilanid is superior to the ordinary digitalis, as the same potency can be expected in equivalent weight doses with any random sample of the drug dispensed. However, it should be remembered that *the dosages required for therapeutic effect depend not only on the potency of the drug employed, but also on the individual sus-*

ceptibility and tolerance. These biological variants are in the last analysis the most important determinants of the dose employed in each individual case.

Digilanid is a stable preparation, easily absorbed, and rapidly effective. The rate of elimination and the degree of cumulation are closely similar to those of ordinary digitalis. Its therapeutic range assures safety of administration. The indications for its use, as well as its limitations, are those of digitalis therapy in general.

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CHAPTER III

Lanatoside C

Of the constituents of Digitalis lanata two glycosides, lanatoside C (cedilanid) and digoxin, have been studied quite extensively. These preparations are closely related to each other, digoxin being a degradation product of lanatoside C. However, they differ somewhat pharmacologically. Of the two, lanatoside C has been the subject of most extensive research in this country. It promises to be one of the most useful cardio-active principles known. Although one of the more recently discovered chemically pure cardiac glycosides, it has promptly attained a prominent position in the specific therapy of heart disease.

Chemical Structure

In the preceding chapter the similarities of and the differences between Digitalis purpurea and Digitalis lanata have been discussed. It has been pointed out that each had three glycosides, but that lanatoside C could not be found in the leaves of Digitalis purpurea. While lanatoside A is closely related to digitoxin which is derived by hydrolysis from one of the glycosides in the ordinary digitalis purpurea, and lanatoside B is also closely related to one of the native glycosides in the ordinary purpurea, lanatoside C has no close chemical counterpart in the ordinary digitalis.

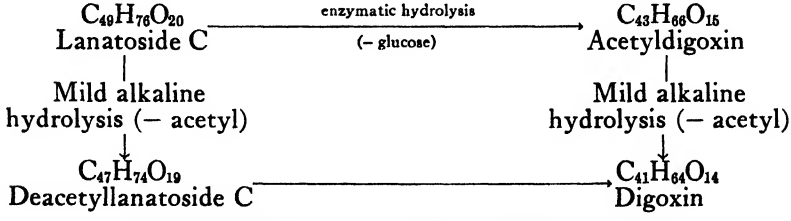
Lanatoside C is a pure substance possessing a characteristic crystalline form with a melting point of 245–248°. It is easily soluble in methyl or ethyl alcohol. Although only slightly soluble in water, this solubility suffices for its therapeutic use. The empiric formula is $C_{49}H_{76}O_{20}$.

On enzymatic and alkaline hydrolysis the glucose and acetyl radi-

cles are liberated, leaving the glycoside digoxin. Further acid hydrolysis splits off three molecules of pentose sugar (digitoxose) from the aglucone digoxigenin, the active cardiac principle.

TABLE VI

DEGRADATION OF LANATOSIDE C TO DIGOXIN



A. Stoll, *The Cardiac Glycosides*, the Pharmaceutical Press, London, 1937.

From Table VI it can be seen that in contrast to alkaline hydrolysis, with the aid of enzymes, the pure lanatoside C yields in addition to glucose the acetylglycoside. With both enzymatic and alkaline hydrolysis the end product is digoxin.

PHARMACOLOGY

Effectiveness and Toxicity of Lanatoside C as compared with Lanatosides A and B

The initial pharmacologic analysis of lanatoside C was carried out by Rothlin.[1] However, a particular interest in this preparation developed as a result of the research by Moe and Visscher, whose work gave considerable impetus to the clinical application of the drug. Moe and Visscher[2,3] made individual studies on the three natural glycosides of Digitalis lanata. Both heart-lung preparations and intact animals were used and the minimum doses producing increased cardiac efficiency as well as those causing toxic effect were determined. The therapeutic action was evidenced by an increase in work, a decrease in venous pressure, diastolic volume and oxygen consumption, and an increase in mechanical efficiency. The toxic stage was considered as reached when irregularities of conduction and rhythm (eventually leading to ventricular fibrillation) had made their appearance. The larger the dose administered, the earlier the toxic stage appeared, but if small enough doses were given, the toxic manifestations were not observed at all. It was found that there was no constant relationship between the toxic and therapeutic doses for the different glycosides. The ratio of the dose causing increased cardiac efficiency (c.e.d.) to the dose produc-

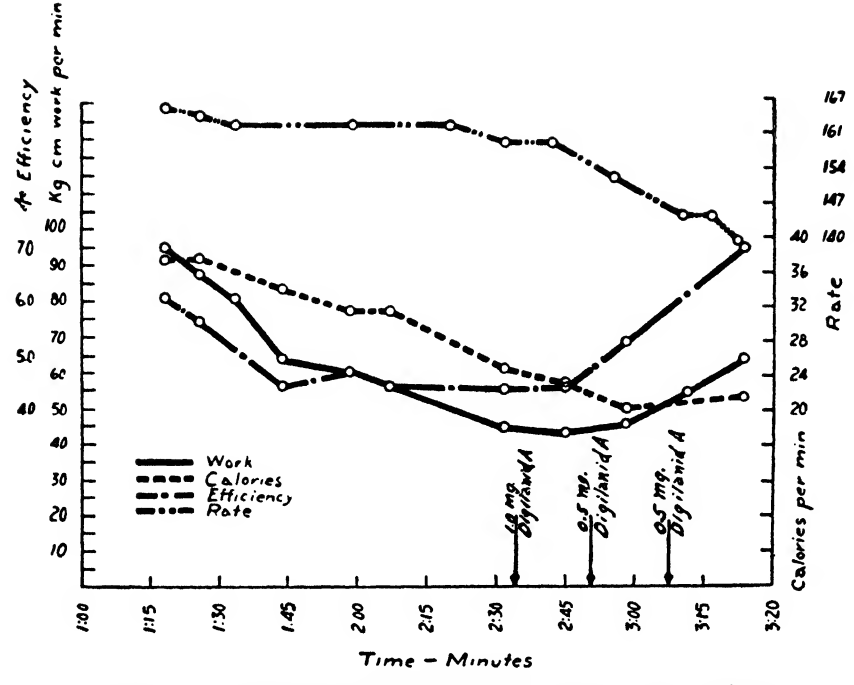


FIG. 12. The effect of 2.0 mg. lanatoside A on energy liberation, work, efficiency, and heart rate in the heart-lung preparation. (From M. Visscher, *Minnesota Med.*, vol. 21, 1938.)

ing irregularities (c.i.d.) differed greatly for the different glycosides. The lethal cat dose (c.d.) did not vary in proportion to the dose increasing cardiac efficiency (c.e.d.). In the course of these studies it was disclosed that the ratios $\frac{\text{c.i.d.}}{\text{c.e.d.}}$ and $\frac{\text{c.d.}}{\text{c.e.d.}}$ were both very much greater for lanatoside C than for the other two glycosides of Digitalis lanata, implying a greater margin of safety for the former substance in accomplishing improved cardiac efficiency. These investigators also discovered that lanatoside C was from five to ten times as potent in producing an increase in efficiency as lanatoside A, for example, and that its effects also came on more rapidly. Different solubility could not account for greater rapidity of action, because the C is less soluble than the A. At the same time the former was found also to be more potent than the B. For instance, the average lethal dose for lanatoside B was .65 mg. per kg. body weight, and the minimum therapeutic dose (one which produces a just increase in efficiency in the heart-lung preparation) 1.0 mg. per kg. of heart, lung, and blood, while in the

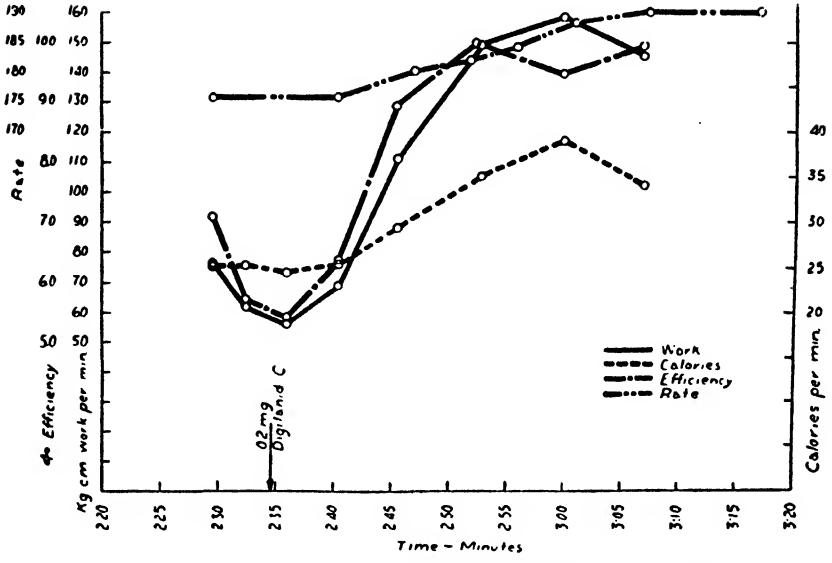


FIG. 13. The effect of 0.2 mg. lanatoside C on energy liberation, work, efficiency, and heart rate in the heart-lung preparation. (From M. Visscher, *Minnesota Med.*, vol. 21, 1938.)

case of lanatoside C, although the average lethal dose was .35 mg. per kg., the minimum therapeutic dose was extremely small, being .02 mg. per kg. Thus, in relation to its toxic or lethal action, the C has 25 times the therapeutic action of the B. Lanatoside A falls between the other two in regard to these actions. The toxic/therapeutic ratios for the three lanatosides were found to be: lanatoside A — 0.85; lanatoside B — 0.4; and lanatoside C — 1.9.[4] Thus Moe and Visscher demonstrated that lanatoside C is not only the most active of the three lanatosides, but also possesses a wider therapeutic range (is less toxic).

Rothlin,[5] who made the initial pharmacological studies on these substances, reported that by the ordinary cat-assay method, lanatoside C is only slightly more active than the A. He found that the A is 1.35 times and the B 1.42 times weaker than the C. By the frog's heart method the A and the B had identical activity. Still clearer were the differences obtained with the aglucones of the lanatosides: Digitoxigenin, the aglucone of lanatoside A, and gitoxigenin, the aglucone of lanatoside B, were found to be more than several times weaker than digoxigenin, the aglucone of lanatoside C.

The difference between results obtained by Rothlin and those of Moe and Visscher, warrants a comment to the effect that the technique Rothlin employed really measures the toxicity of the active principles.

Obviously the toxic dose method does not necessarily parallel the evidence in regard to the therapeutic efficiency. If equally toxic substances may differ in their therapeutic actions, biological assays using the toxic action as the end point may fail to give reliable information in regard to the therapeutic effects. The possible error incurred by translating lethal action on animals into terms of clinical usefulness constitutes the major drawback in the standardization of the potency of crude products, such as whole leaf digitalis, by the presently current method of bio-assay. When Moe and Visscher[4] used the same technique as Rothlin, they also found that the potencies of the three lanatosides, as determined by frog, cat, and pigeon assay, did not differ greatly. Also Kaplan and Visscher[6] demonstrated that the pigeon-emesis method does not distinguish any non-proportional degrees of activity of different glycosides. The differences were discovered only by other methods of study when the effects were evaluated in terms of therapeutic activity upon a dog's heart. It must be conceded that these conditions of experimentation are still far removed from those of clinical experience; however, in principle they are closer to conditions of clinical practice than the methods which attempt to evaluate an active principle on the basis of purely toxic or lethal effects.

The question of whether or not the toxic/therapeutic ratio among different glycosides may vary is still a controversial subject. The interpretation given in this regard by Moe and Visscher has been criticized on the grounds that as they deduced their ratios of toxic to therapeutic dose by relating the fatal intravenous dose in the cat to the dose causing efficiency changes in the heart-lung preparation of the dog, the divergence in susceptibility obtaining from one animal to another, and in the same animal depending on the experimental setup, was not considered.[7,8] There are investigators who still believe that toxic and therapeutic effects are both manifestations of the same fundamental action on the living tissues. Some experimental work lends support to this thesis. Thus Gold *et al.*[9] compared a number of cardiac actions within both the therapeutic and toxic range of widely different digitalis bodies by determining the average percentage of the fatal dose producing the first change in various electrocardiographic signs in cats. They arrived at the conclusion that these different digitalis bodies acted with the same relative intensity. Cattell and Gold,[7] in their studies with the papillary muscle of the cat, found that the lanatosides A, B, and C had about the same potency in reference to both their therapeutic and toxic effects. In their studies on man Kwit, Gold, and Cattell[10] came to similar conclusions by demonstrating that changes in the T wave in the electrocardiogram run parallel with the essential therapeutic action of

digitalis which leads to changes in the heart rate of patients with auricular fibrillation. On the other hand it has been shown by others that differences in therapeutic efficacy of different glycosides of equal dog or cat toxicity exist. Thus, for example, Takahashi *et al.*[11] have shown that there is no constant relation for different glycosides between the dose increasing contraction amplitude in the rabbit heart and that producing cardiac standstill.

Aside from the controversial question of toxic/therapeutic ratios, the order of activity for the three lanatosides of Digitalis lanata as found by Moe and Visscher has been corroborated by others. Moe and Visscher[1] found that the minimum dose of lanatoside A which brought about improvement in cardiac efficiency was 1 mg.; of lanatoside B 2 mg.; and of lanatoside C 0.04 mg. This represents considerable difference in activity. Similarly in cats, Chen, Hargreaves, and Robbins[12] found the order of activity highest for lanatoside C, lowest for the B; and intermediate for the A.

Evidence indicating that there may be not only quantitative but possibly even some qualitative differences in cardiac action of different cardiac glycosides is suggested by the work of Rall, Wells, and Dragstedt[13] on the abolition by the active principles of the cardiac inhibition produced by acetylcholine. While lanatoside C invariably abolished this cardiac inhibition by acetylcholine, lanatosides A and B exhibited such action inconstantly. If not of really qualitative significance, these findings may be interpreted to signify at least a quantitative difference in cardiac effect, since the same fraction of a lethal dose in case of each glycoside was employed. If so, it serves as additional evidence in support of the view above presented, upholding a difference of degree of therapeutic action within the same range of toxicity.

Effects on the Heart and Circulation

La Due and Fahr,[14] on administering lanatoside C to patients with heart failure and normal sinus rhythm demonstrated an increase in the pulse pressure, increase in the velocity of circulation and reduction in the venous pressure within two hours after administration of the drug. Roentgenkymographic studies showed that the glycoside produced a significant reduction of diastolic heart volume. By using the Keys and Friedell formula for estimating stroke output from the roentgenkymogram, the authors found an increase in stroke volume. Since the diastolic heart volume is an index of oxygen consumption,[8] these increases in work which resulted from the administration of lanatoside C must have represented proportional improvement in the mechanical efficiency of the heart. The most consistent and lasting change in the fail-

ing heart resulting from the drug action seemed to be a decrease in its diastolic volume. Increase in circulatory velocity and decrease in venous pressure in congestive failure were also found by Hrenoff.[15] Comparable results were obtained by many different investigators.[15a]

Eichna, Taube, and DeGraff[16] injected Lanatoside C intravenously into normal subjects and found small to moderate changes in the electrocardiogram and in several circulatory functions. In the electrocardiogram the most frequent alteration consisted of a decrease in the amplitude of the T waves in one or more leads. Occasionally the RS-T segment became slightly depressed and the P-R interval slightly prolonged. Initial changes usually appeared within ten to fifteen minutes; maximum effects in one to six hours. The circulatory changes were usually small, never more than moderate. Typical, full responses consisted of a prompt, at times considerable, decrease in heart rate; a slight to moderate increase in stroke volume, and a small rise of arterial pressure, largely systolic. As the decrease in heart rate was proportionately greater than the compensatory increase in stroke volume, the minute output usually decreased. The effects on the electrocardiogram and the circulation were not always related to each other, the two changes often, but not necessarily always, appearing concomitantly. While atropinization had no effect on electrocardiographic changes which were apparently due to direct cardiac action, it would raise the heart rate to the level found prior to administration of the glycoside. Thus the glycoside-induced decrease in heart rate must have been due to the influence of the drug via the vagus nerve.

Kwit, Gold, and Cattell[17] found that Lanatoside C produces the characteristic digitalis-like changes in the electrocardiogram. Tandowsky[18] found that the average time required for the development of maximal RS-T segment changes in normal subjects after administration of 1.6 mg. of lanatoside C intravenously was twenty-seven minutes. In patients in congestive failure the changes were produced in two to three hours after intravenous administration. In normal subjects the RS-T segments returned to normal in about sixteen hours.

Essex, Herrick, and Visscher[19] found by inserting a thermostromuhr into the coronary arteries of dogs that lanatoside C (as well as the A and B) administered in sub-nauseating doses had no effect on the mean coronary flow.

Fahr and La Due[20] in the course of their clinical studies arrived at the conclusion that lanatoside C ' seems definitely less toxic than preparations of Digitalis purpurea.' Tandowsky,[18] from his observations on normal controls and cardiac patients, also draws the conclusion that

' unlike Digitalis purpurea, lanatoside C does not produce untoward effects . . . and seems to lack the nausea producing elements of the whole leaf.' He thought that the rapid elimination of the drug accounted for these differences. Margolin[21] reports a patient with rheumatic heart disease, auricular fibrillation, and congestive failure, unable to tolerate Digitalis purpurea, but who responded promptly and effectively to lanatoside C. Similar findings of relatively lower toxicity have been made by other workers. However, these enthusiastic reports should not lead to the erroneous belief that danger of toxicity from excessive doses does not exist; for such untoward effects may appear with all cardio-active principles without exception. They may be regarded as representing an extension of the beneficial action beyond the zone of therapeutic usefulness.

Myocardial necrosis and fibrosis noted in the hearts of animals receiving toxic doses of other digitalis bodies have also been observed as a result of administration of toxic doses of lanatoside C. However, La Due[22] reports that the heart muscle was found to be histologically normal in a dog when complete digitalization doses were administered intravenously every day for thirty days. This is equivalent to the amount given intravenously for complete digitalization in man and would never be given daily. Also oral doses of five times the therapeutic amount were given dogs daily over periods of one to three months without producing any abnormalities in the myocardium on histological examination. The same author made observations that the drug can be given to man over a long period of time without the danger of producing morphologic changes in the myocardium.

It will be remembered that potassium plays an important role in cardiac physiology. In this connection it is interesting to note the work demonstrating the effect the glycoside has on the potassium content of the heart muscle. Hagen[23] found in a series of isolated rabbit hearts that ' therapeutic ' doses of lanatoside C caused a slight increase in heart muscle potassium, while the toxic doses produced a marked decrease.

Interesting studies have been made by Crismon and Elliott[23a] on the effect of lanatoside C upon the survival of experimental animals subjected to severe hypothermia. This work has served as a continuation of earlier studies on this subject by other investigators. As the arrest of respiration before the cessation of heart beat has been the usual course of events in death from hypothermia, it had been concluded that the fatal outcome was due to respiratory failure. However, other workers have shown that circulatory failure appeared to be the cause of death from hypothermia in experimental animals. Moreover, in the dog, digitalis has been noted to be

effective in preventing circulatory failure during cooling. However, none of the human victims of German experiments on hypothermia responded favorably to intravenous injection of strophanthin. Talbott has stated that: '. . . most patients who die after exposure suffer from terminal cardiac failure.' Crismon and Elliott have formulated the following stand, which served as the basis for their experiments: If the failure in respiration in hypothermia is brought about by a direct influence of low temperature, improvement of circulation alone would not prolong the survival of animals; on the other hand, if failing circulation is the primary factor leading to failure of the respiratory function, then animals in which failure of the circulation is prevented or postponed should survive the reduction of their body temperatures to levels lower than those tolerated by untreated controls. The data presented by these workers include observations of respiration, heart rate, arterial pressure, and the electrocardiogram of rats during induced hypothermia, and the modifications of the response to cooling subsequent to the intravenous administration of lanatoside C. The rats treated with the cardiac glycoside have exhibited a number of signs of improved ability to withstand the effects of lower body temperature; the minimum lethal temperature was 2 to 5° C. lower for the treated rats than for the control ones; terminal pulmonary edema, frequently observed in untreated controls, was rarely seen in the treated animals; rats treated with lanatoside C showed fewer disturbances of rhythm and conduction. The authors have concluded that the respiratory failure in hypothermia is relatively independent upon the body temperature and is, instead, dependent upon the level of perfusion pressure in the circulation. The results of these experiments would tend to give support to the statement by Talbott, mentioned above, that the patients who die after exposure suffer from terminal cardiac failure. Were the circulatory collapse of peripheral origin rather than due to cardiac failure, one would be less prone to expect beneficial effects from digitalization.

Absorption, Elimination and Cumulation

Dille and Whatmore[24] in their studies on animals concluded that the greatest absorption of the drug takes place in the intestine, but that some of the drug is also absorbed from the colon and stomach. They thought that there is a partial destruction or inactivation of the active principle in the lumen of the gastro-intestinal tract.

No more is known about the fate of the glycoside after absorption than in the case of digitalis. DeGraff and Lehman,[25] using the procedure applied by various investigators in the study of cumulation and rate of elimination of the digitalis bodies,* found that the lethal effect

* It consists of injecting intravenously an accurately measured sublethal dose of the glycoside to be studied and after varying time intervals infusing ouabain until the death of the animal.

of lanatoside C dissipates rapidly during the first twenty-four hours after intravenous injection in cats. The lethality of digoxin (the glycoside obtained by partial hydrolytic cleavage of the genuine glycoside), however, actually increases during the first three hours and is still quite strong after twenty-four hours. The effect of digoxigenin (the aglucone) completely disappears in twenty-four hours.

Kwit, Gold, and Cattell,[17] in their studies on potency and dosage of lanatoside C in man, concluded that the drug was poorly absorbed from the gastro-intestinal tract. They based this assumption on their finding that the maintenance dose of digitalis, as measured in cat units, was smaller than the equivalent dose of the glycoside (1 or 2 cat units of the former as compared with 4.5 units of the latter). In addition they found that five to ten times as much of the drug was needed to digitalize by oral route as intravenously. DeGraff and Batterman[26] believe that these results could be explained adequately by rapid elimination rather than poor absorption, as with a rapidly eliminated drug the excretion of some of the active principle may well occur before all of it is absorbed from the digestive tract. The experimental evidence that the glycoside is rapidly eliminated has already been presented.[25] In addition there are also some clinical indications to the same effect. Thus, Fahr and La Due[20] found that in a number of patients in whom nausea and occasional vomiting occurred during the course of treatment with lanatoside C, on further administration of the same dosages in spite of these symptoms, both nausea and emesis ceased. The fact remains that no difficulties are encountered in achieving full effect with oral administration of the glycoside.

In concluding the discussion of pharmacological properties of lanatoside C it may be pointed out that it has a strophanthin-like effect due to its rapidity of action and somewhat weaker cumulative ability. At the same time it has the advantage over strophanthin because it is effective orally. In addition, there is some evidence to the effect that the therapeutic/toxic ratio may be more favorable in the case of lanatoside C as compared with the latter drug.

Standardization and Preparations

As lanatoside C is a pure chemical substance it is standardized by gravimetric method, thus circumventing the undesirable features of bio-assay discussed in the chapter on Digitalis purpurea. According to Rothlin,[1] 0.28 mg. of the drug is equivalent to one international Magims-DeLind cat unit. It is marketed under the commercial name of 'Cedilanid' for oral and parenteral administration. For oral use there

are available tablets of 0.5 mg. For injection there are ampules of 2 cc. and 4 cc. size containing 0.4 mg. and 0.8 mg. of the glycoside respectively. No instances of thrombosis following intravenous injection have been reported. Neither have any dangerous complications been observed from injection of the drug intravenously in appropriate doses. Suppositories of cedilanid are available and frequently employed in Europe, but not in this country.

Friedman and Bine[26a] have employed the embryonic duck heart for the detection of minute amounts of lanatoside C. Their work was undertaken in an attempt to devise a method which would make possible the demonstration of digitalis effect in the presence of minute fractions of the cardio-active principle. Such a technic would lead to more exact quantitative information concerning the absorption and excretion (or destruction) of the digitalis group of drugs in the human body. The absence of any tests sufficiently sensitive to detect the relatively minute amounts of cardio-active principles which must be present in the tissues and fluids of patients receiving the drug has interfered with the acquisition of exact data on this subject. Other bio-assays (frog, cat, and pigeon methods) have been limited to the quantitation of relatively large amounts of the active principles. These authors have found that the embryonic duck heart was far more sensitive to the digitalis glycoside employed than the embryonic chick heart. The latter organ had been employed by Pickering in his attempt to find a method of bio-assay which would allow the detection of small amounts of cardiac principles. In the method of Friedman and Bine, the first indication of sensitivity of the embryonic tissue to the cardiac glycoside was an acceleration and an intensification in the vigor of cardiac contractions as observed through the microscope. The auriculoventricular block was used as the actual indicator for the presence of the drug. In their work with the embryonic duck heart, Friedman and Bine have been able to detect lanatoside C in amounts of 0.1 cc. of a 1 to 20 millionth dilution (0.000005 mg.). This appears to be the most sensitive method for the detection of a digitalis glycoside yet described. The same authors,[26b] by using this technic, obtained evidence that the embryonic duck heart exhibits a digitalis effect of lanatoside C with no fixed latent period. They concluded that: 'It would appear that if a sufficient quantity of digitalis glycoside is present, a digitalis effect may be expected almost immediately.'

Clinical Applications

Heart Failure

Kwit, Gold, and Cattell[17] in the course of clinical studies concluded that the dosage of lanatoside C predicated on the basis of the frog or cat methods of assay was not applicable to its oral administration in man. When given orally, the cat unit of lanatoside C was found to be

about one-half as potent in man as the cat unit of digitalis leaf. The authors thought that the range between the therapeutic and toxic doses of the glycoside in man was similar to that for the ordinary digitalis (and digitaline Nativelle). They found that the oral dose which produced and maintained full therapeutic effects without toxic symptoms varied in most cases between six and ten cat units (1.5 to 2.5 mg.) daily, while the full digitalization dose by intravenous injection was about six cat units (1.5 mg.) given within about two to three hours.

Fahr and La Due[20] from their observations found that lanatoside C when administered intravenously to patients with auricular fibrillation reduced the heart rate to normal within a period of two minutes to two hours. With oral administration this change took place within twenty-four to forty-eight hours. The drug was also efficacious in the treatment of congestive heart failure when regular rhythm was present. They concluded that the efficacy of lanatoside C in the presence of normal sinus rhythm was 'almost as great' as when the heart failure was associated with auricular fibrillation. The authors were impressed by comparative rarity of toxic reactions to the drug, referring to this as being 'striking.' There was not a patient who was unable to take the drug, and only eight patients among the 256 could not tolerate the usual doses because of intractable nausea or vomiting. However, when the drug was withheld for two days in these eight patients and then given in doses of one tablet per day, the symptoms failed to recur and the expected therapeutic result was attained.

Sokolow and Chamberlain[27] studied the action of lanatoside C in patients who presented the usual indications for digitalis therapy, such as congestive heart failure with normal sinus rhythm or auricular fibrillation and paroxysmal nocturnal dyspnea. The drug was given both orally and intravenously and repeated electrocardiograms were taken. Dosage varied in accordance with the speed desired for digitalization. The maintenance dose for both oral and intravenous administration was determined by frequent re-examination of patients over a period of months. The authors considered the maintenance dose as that amount of the drug just short of the point of mild toxic symptoms which could be maintained for at least one month. The authors concluded that the therapeutic results with lanatoside C paralleled the best previously obtained with ordinary digitalis.

About 40 per cent of the patients studied by Sokolow and Chamberlain had heart failure with regular rhythm. Striking therapeutic benefits were achieved in all but three of these cases. There resulted

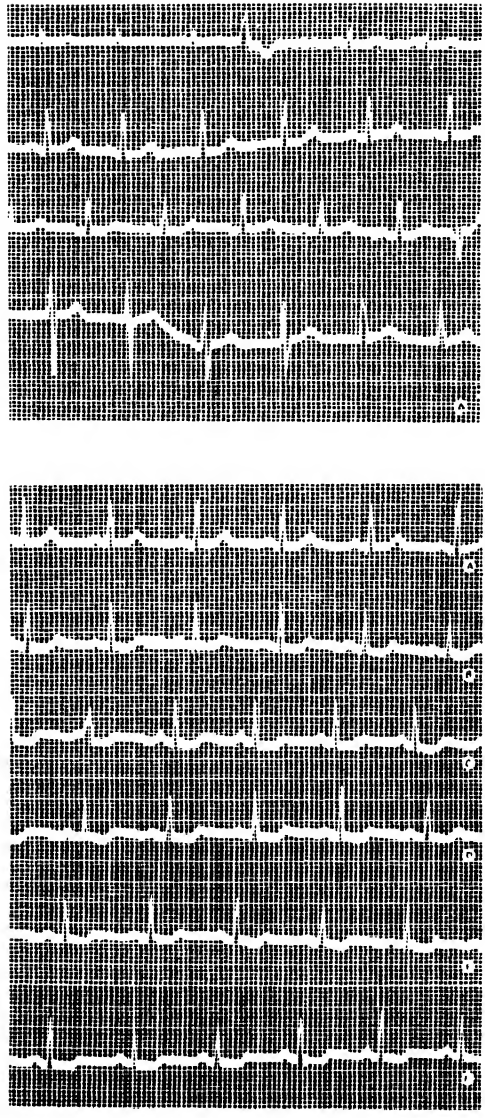


FIG. 14. Effect of lanatoside C, intravenously, on normal myocardium. *Above.* Standard electrocardiographic leads on normal prior to administration of lanatoside C — 1.6 mg. intravenously. *Below.* Serial tracings taken in Lead 2. A, at time of injection of 8 cc. of lanatoside C; B, fifteen minutes later; C, thirty minutes later; D, one hour twenty minutes later; E, one hour thirty minutes later; F, two hours later; digitalis effect receding. (From R. M. Tandowsky, *Am. Heart J.*, vol. 24, 1942.)

an almost uniform improvement in all the signs and symptoms of failure, such as dyspnea, orthopnea, or edema. About one-third of the patients had auricular fibrillation (with or without failure). All of them showed a definite improvement. The oral dose required for full digitalization effect varied from 7 mg. in twenty-four hours to 16 mg. in ninety-six hours; the average dose was 7.5 mg. in seventy-two hours.

The drug was administered intravenously in full dosage to forty-one patients. Digitalization was accomplished by single or multiple injections within twenty-four to forty-eight hours. The full digitalizing dose varied between from 6 to 16 cc. (1.2 to 3.2 mg.) in twenty-four hours. No patients were found to have even mild toxic reactions on less than 8 cc. (1.6 mg.) in twenty-four hours. Three patients who received 8 cc. in one single injection developed mild transient nausea. Several patients who were given 2 cc. (0.4 mg.) every four hours required three to four days for full digitalization effect. There were no toxic symptoms and the results were excellent. Quite striking clinical effects were observed with intravenous administration. Although the full effect took place only within an hour, an abrupt slowing of the cardiac rate not infrequently occurred in ten minutes after injection. However, in a number of patients, significant slowing resulted only after saturation had been reached. Noteworthy were the observations on patients who entered the hospital in desperate condition, in far advanced stages of congestive failure and who within a period of only twenty-four hours showed marked subjective and objective improvement. For intravenous administration the authors chose a procedure consisting of an initial dose of 6 cc. (1.2 mg.) followed by doses of 2 cc. (0.4 mg.) every three to four hours until the desired therapeutic effect or the toxic mild symptoms were observed.

No significant differences in clinical effectiveness of oral and intravenous administrations could be determined; however, a difference was noted with regard to the speed of effect. Also with the oral drug toxic symptoms were more marked. It was also found that patients saturated with lanatoside C could be maintained on Digitalis purpurea and vice versa.

In a number of cases data were obtained by Sokolow and Chamberlain on the comparative maintenance doses of lanatoside C and the ordinary digitalis. The average maintenance doses were 1.6 mg. for the glycoside and 0.13 gm. for Digitalis purpurea. This is equivalent

to a ratio of five to one in terms of cat units.* The authors also found that the ratio of full digitalization dose to the maintenance dose was 8.6:1.6, or 4.7, for the glycoside and 1.5:0.13, or 11.3, for Digitalis purpurea. In other words, the maintenance dose of lanatoside C is approximately one-fourth of the digitalizing dose, while with ordinary digitalis it is one-eleventh the digitalizing dose. This may be interpreted to signify that the glycoside administered orally is either absorbed or 'spent' (utilized) roughly three times faster than oral digitalis. It was computed that approximately 2.8 times as much lanatoside C is required for oral as for intravenous twenty-four-hour digitalization. This seems to bear out the contention of Gold and collaborators[17] that the glycoside is not absorbed completely from the digestive tract.

In their later work, Chamberlain and Sokolow[28] concluded that a satisfactory method for administration of lanatoside C by mouth consisted of giving 6 to 7.5 mg. in about seventy-two hours (twelve to fifteen tablets). Four mg. (eight tablets) can be given on the first day in divided doses and 2 mg. (four tablets) daily thereafter. On attainment of full therapeutic effect or the appearance of initial toxic manifestations, the dosage should be decreased. The final conclusions drawn by these investigators were to the effect that standardization of lanatoside C by weight 'appears to be advantageous because it insures constant potency, the lack of which is a recognized disadvantage of Digitalis purpurea. . . . The rapid absorption, constant potency, and rapid action of cedilanid give it advantages over Digitalis purpurea.'

Parsonnet and Bernstein[29] selected for their study a mixed group of hospital out-patients, hospital ward patients, and private ambulatory and bed-ridden patients. Seventy-five per cent had been receiving digitalis for varying periods. In these patients the difficulties in controlling their maintenance dosage with digitalis were well realized. The remaining 25 per cent had never taken digitalis. The authors found the average total dose required for digitalization with lanatoside C by mouth to be 7.5 to 10 mg. (fifteen to twenty tablets). For the rapid method of digitalization the total dose was approximately 5 to 7.5 mg. (ten to fifteen tablets). The criteria for improvement were disappearance of signs of failure, such as dependent edema and ascites with enlarged liver, slowing of the cardiac rate, decrease in venous pressure

* It should be noted that the comparison in terms of cat units is not valid between a pure chemical substance (lanatoside C) on the one hand and a crude product (ordinary digitalis) on the other hand.

and electrocardiographic evidence. Ninety-eight per cent of the patients responded to oral administration of lanatoside C very satisfactorily. The authors thought that the beneficial effect was attained sooner than when Digitalis purpurea was employed, and that the glycoside was eliminated more rapidly. Noteworthy was their observation that once a maintenance dose was established, it could be continued indefinitely, provided the same conditions prevailed (change in patient's activities or occurrence of coronary occlusion). Two of the hundred patients thus studied, both of whom had auricular fibrillation of long standing, could not be controlled by lanatoside C (even with the daily dose of 3 mg.). They responded well to ordinary digitalis. The authors concluded that although the same toxic effects can be produced with lanatoside C as with Digitalis purpurea, nevertheless the margin of safety was greater with the glycoside. In addition they felt that the rapid elimination of the latter diminished the duration of toxic symptoms. They also remark that the worry that each new prescription may be stronger or weaker is eliminated, as the pure substance standardized by weight is, of course, not subject to the variations of bio-assay. On the other hand, however, DeGraff and Batterman[26] believe that it is somewhat more difficult to keep a patient on a proper therapeutic level with lanatoside C because of more rapid elimination.

La Due[30] states that in patients with heart failure and auricular fibrillation the intravenous dose needed to reduce the ventricular rate to 85 beats per minute or lower, 1.6 mg. (8 cc.) of lanatoside C are required. By oral route the dose necessary to produce similar results was 6.25 mg. within twenty-four hours. The average maintenance requirement varied between 0.5 and 1.25 mg. daily, the larger amount (1.25 mg.) usually being necessary during the period of congestive failure. The author noted that if this dosage is still continued after compensation has been regained, occasionally toxic symptoms may be observed. The author gave lanatoside C intravenously to eighty-three patients with congestive failure. Sixty-two of the patients had auricular fibrillation and twenty-one had a regular rhythm. The etiological factors were hypertension, degenerative or valvular disease. In another group of eighty-five patients with both sinus rhythm and auricular fibrillation, the drug was given orally. Of fifty-two patients with heart rates above 120, 78 per cent responded to intravenous medication in less than two hours with the slowing of ventricular rate to 85 or lower; two required thirteen to twenty-four hours; two, twenty-

five to forty-eight hours; and two, forty-eight to seventy-two hours. Detailed study of fifteen patients revealed that the pulse slowed to eighty-five or less in from two to ninety minutes, the average period being thirty minutes.

The patients who received the drug orally (6.25 mg.) within a twenty-four hour period responded with a slowing of the heart rate within twenty-four to forty-eight hours after the initial dose, while patients receiving the drug intravenously promptly reported marked subjective improvement; those taking the drug orally had to wait for twenty-four to forty-eight hours before noticing any significant changes. There was no significant difference in the average rate of improvement as measured by decrease in venous pressure, increase in circulatory velocity, rise in vital capacity, and onset of diuresis.

Nicholson[81] reports similar favorable response to intravenous administration of lanatoside C and remarks that the drug can be administered intravenously 'with wide margin of safety, requires no fractional dosage, and is rapid in action. It appears to have a definite advantage over the glycosides of D. purpurea.'

Eichna and Taube[82] made observations on the same patient with moderately severe congestive failure and auricular fibrillation (with rapid ventricular rate) to whom several cardiac glycosides were given successively in equivalent molecular amounts (lanatoside C — 0.63 mg.; digoxin — 0.5 mg.; digitoxin — 0.5 mg.; and ouabain — 0.375 mg.). Comparing the effects obtained, molecule for molecule, they found that ouabain initiated effects most rapidly, and digitaline Nativelle (digitoxin) most slowly. Between the two, but resembling ouabain more closely, were lanatoside C and digoxin; the latter was slightly more rapid in its action.

Although there is still some doubt as to the value of digitalization of cardiac patients in whom the usual symptoms and signs of heart failure have not developed, attempts have been made by a number of investigators to digitalize such patients 'prophylactically' not only with the official digitalis (see chapter on Digitalis folium) but also by employing the pure principles. Thus Erickson and Fahr (32a) have administered lanatoside C to patients with organic heart disease in the compensated state. Of 39 patients with clinically compensated, but organically diseased hearts, 34 (87 per cent) showed definite improvement in mechanical efficiency upon the administration of full digitalizing doses of the glycoside. The remaining 5 patients who failed to show any significant improvement were not made worse. At the same

time, 14 persons with normal hearts showed a definite impairment in cardiac function after the administration of the drug.

In patients who benefited by treatment the improvement was greatest when the circulation time was prolonged from 16 to 22 seconds. The response was essentially the same in hypertensive and rheumatic heart disease and coronary sclerosis. The authors felt that in the compensated organically diseased heart the drug increases the mechanical efficiency so that a greater percentage of the total energy liberated is converted to mechanical work as in the case of failure. They concluded that digitalization is definitely indicated for organically diseased and enlarged hearts which appear compensated when the circulation time (arm-to-tongue) is greater than 16 seconds. The question arises as to whether or not a patient with organic heart disease who already has cardiac enlargement accompanied by some prolongation of circulation time can still be considered to be in a compensated state.

Cardiac Arrhythmias

Lanatoside C has been found to be effective in auricular fibrillation as well as in other arrhythmias. Fahr and La Due[20] were able to ascertain the efficacy of the drug in treatment of paroxysmal tachycardia of supra-ventricular origin, such as auricular tachycardia and flutter. Five patients with paroxysmal tachycardia of supra-ventricular origin responded promptly to an intravenous injection of 8 cc. of the drug. Normal sinus rhythm was established within five minutes in two cases; within ten minutes in another; and within two hours in two more. In one case of paroxysmal auricular tachycardia associated with recent myocardial infarction neither lanatoside C or quinidine was effective. The patient finally succumbed during an attack of ventricular tachycardia ten days after lanatoside C had been discontinued. Four patients with auricular flutter were successfully treated. They showed 2:1 block in the electrocardiogram and had ventricular rates of 188 and 162 respectively. Both received 8 cc. intravenously. Normal sinus rhythm was restored in the first case within five minutes, and in the second case within eight minutes. In neither case did the mechanism pass through the state of auricular fibrillation before normal rhythm was established. The third patient, a young girl with congenital heart disease, had auricular flutter for more than one year. Both digitalis and quinidine failed to bring about the desired results and the patient was given two tablets of lanatoside C daily. Two months later the electro-

cardiogram showed normal sinus rhythm. In another case with an auricular flutter and a variable block of 2:1 and 3:1, full digitalization proved unsuccessful. The patient was then given 1.25 mg. of lanatoside C daily, and thirteen days later the flutter changed to fibrillation with a ventricular rate of 45. Another patient with auricular flutter and 2:1, 3:1 block (no heart failure was present) received 8 cc. of the drug intravenously, followed by three tablets daily, and on the fourth day developed auricular fibrillation. In a sixty-seven-year-old man with coronary thrombosis and auricular flutter, lanatoside C proved to be of no avail, and the patient died eight days after the administration of the drug. Seven patients with paroxysmal auricular fibrillation of one to four days' duration were given 8 cc. of lanatoside C intravenously. In four, normal sinus rhythm was restored within ten minutes, and in the remainder within twenty-four hours. In addition, in eight patients with auricular fibrillation of long standing, normal rhythm also was established. An occasional reversal to sinus rhythm in patients with auricular fibrillation treated by digitalis has already been mentioned in the first chapter.

Sokolow and Chamberlain[27] treated seventeen patients with auricular flutter. After administration of lanatoside C in the same doses employed by the authors in patients with congestive failure, conversion to auricular fibrillation occurred in two, and to sinus rhythm in fourteen patients. In the remaining, one conversion was spontaneous. The effect frequently was noted within twenty-four hours.

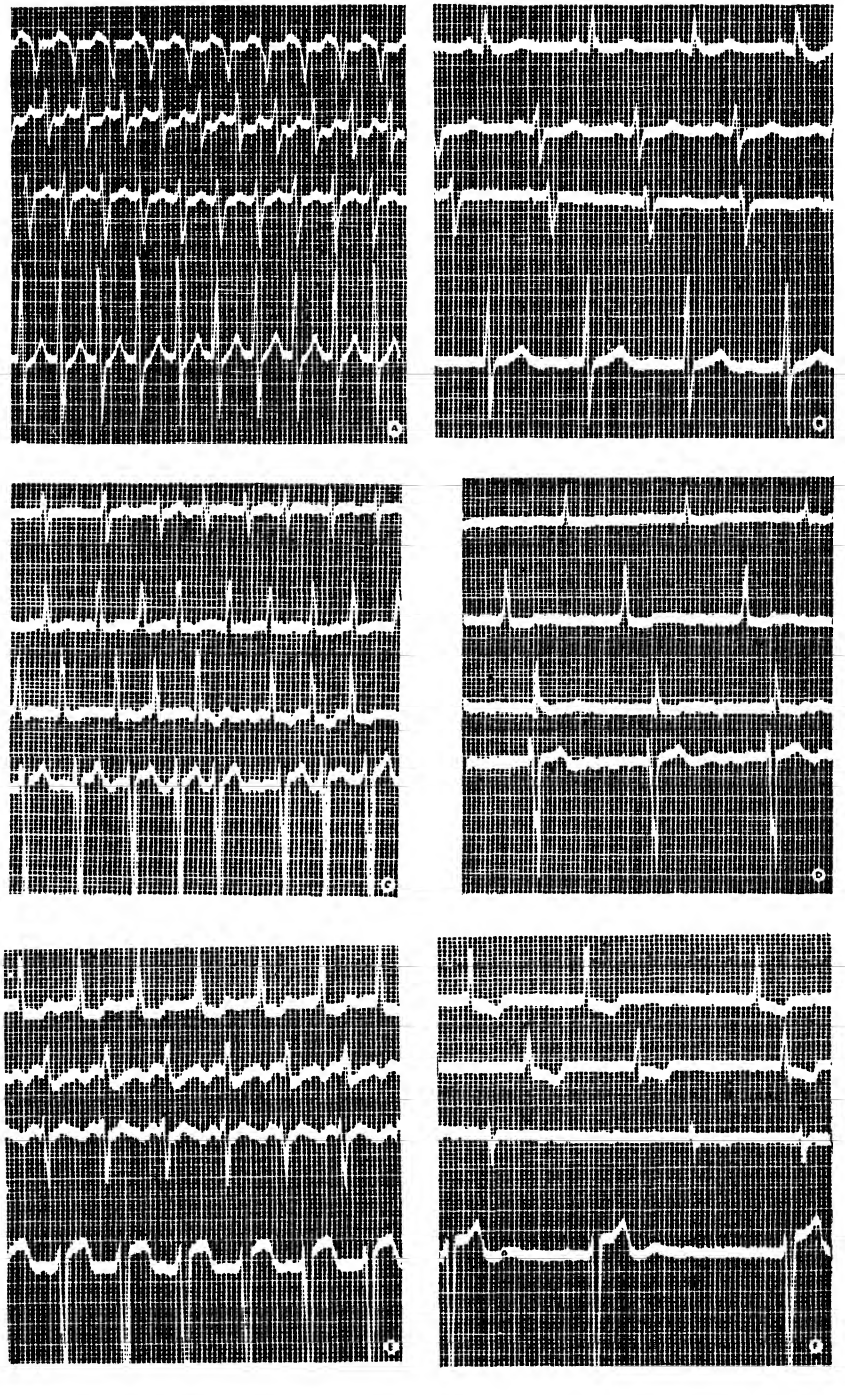
Our own experience with one patient is worth mentioning. There was an auricular flutter with 2:1 block and a ventricular rate of 120. Large doses of quinidine or digitalis proved unsuccessful. Lanatoside C when given in doses ordinarily employed also failed to produce any change. Finally ' heroic ' doses of the glycoside were administered in the amount of 2 mg. (four tablets) four times daily. After the patient had received a total dose of 16 mg. (thirty-two tablets) within a period of only forty-eight hours, conversion to auricular fibrillation with a ventricular rate of 68 took place. This patient demonstrates the extreme variability in individual tolerance to the drug, as he complained of no toxic effects after such a huge dose. It also shows that massive dosages have to be given in certain instances of auricular flutter in order to achieve the expected results.

Tandowsky[88] has reported on the prophylactic use of lanatoside C in patients suffering frequent recurrences of paroxysmal auricular arrhythmias. The study was made on six patients with paroxysmal au-

ricular flutter and two patients with attacks of paroxysmal auricular tachycardia. This series included one case of rheumatic heart disease, four with coronary arterial disease, while in the remaining three there was no evidence of any organic involvement of the heart. The average group age was about fifty years and the average period of observation was approximately fifteen months. Each patient was seen during the attack which was treated with full digitalizing dose of lanatoside C (1.6 mg.) intravenously with one exception where the drug was given orally (6.5 mg.) over a period of forty-eight hours. Reversal to normal sinus rhythm occurred in all within a period of forty-eight hours. While prior to the medication the entire group averaged about four paroxysms of the arrhythmia in the course of twelve months, maintenance therapy with lanatoside C over a period of fifteen months reduced the incidence of recurrence to 0.37. The maintenance dosage in all but one did not exceed 0.5 mg. daily, being 1 mg. in the case of the exception noted. Three patients had one recurrence of tachycardia during the period of observation. In one a paroxysm followed an alcoholic debauch, in another it followed the discontinuance of the drug for one week, and in the third the attack recurred following a laparotomy. The electrocardiographic evidence of glycosidal action was noted in the changes involving the RS-T segments and T waves. Associated cardiac disease had no effect on the results. The only untoward effect consisted in occasional appearance of premature ventricular contractions. The author concluded that lanatoside C 'appears to be of value prophylactically in those subject to recurrent attacks of paroxysmal auricular tachycardia and flutter provided it is used initially in the abolition of an active paroxysm.'

Weisberger and Feil[33a] have treated with lanatoside C, given intravenously, thirteen patients with prolonged refractory paroxysmal auricular tachycardia. The ages ranged from 6 to 69 years. Seventeen paroxysms occurred in this group of cases; ten of the fourteen patients had organic heart disease. The diagnosis was confirmed electrocardio-

FIG. 15. A. Paroxysmal auricular tachycardia resistant to treatment with large oral doses of quinidine, 54 gr. to 60 gr. daily. (Prior to use of cedilanid similar attacks in the same patient could be terminated only by intravenous administration of quinidine, a time-consuming procedure.) B. Regular rhythm after intravenous administration of 6 cc. (1.2 mg.) of cedilanid. C. Auricular fibrillation before, and D. after intravenous administration of 8 cc. (1.6 mg.) of cedilanid. E. Auricular flutter resistant to full therapeutic dosage of digitalis, verging on toxic doses, and equally resistant to treatment with cedilanid in doses ordinarily effective in most cases. F. Conversion to auricular fibrillation with slow ventricular rate after oral administration of four pills of cedilanid four times daily for two days (a total of 16 mg.). This patient shows marked tolerance to the drug. He exhibited no toxic manifestations.



graphically in all cases but one. Electrocardiograms, likewise, were taken during cessation of the attack in all cases but one. In all instances the attack was of prolonged duration and did not respond to repeated attempts at reflex vagal stimulation. The patients found to be refractory were given 0.8 mg. (4.0 cc.) of lanatoside C intravenously. If no satisfactory response occurred within thirty minutes to an hour, another 0.8 mg. was given intravenously. No other medication was employed. In sixteen cases the paroxysmal tachycardia ceased abruptly within forty minutes after the administration of the first dose of digitalis glycoside intravenously. The time of response, excluding one case of thyrotoxicosis with delayed response of twelve hours, varied from four minutes to forty minutes and the average response was 17.6 minutes. Ten patients responded to a dose of 0.8 mg. of lanatoside C, four patients to 1.6 mg., one patient to 1.0 mg., and one patient to 0.4 milligram. No toxic reactions or undesirable side effects were observed. In five patients carotid sinus pressure was applied at varied intervals after the administration of the drug and in each case the paroxysms ceased abruptly, although repeated application of carotid sinus pressure previous to the injection of lanatoside C was ineffective. Thus, marked delay in response occurred only in the patient with thyrotoxicosis. There was no correlation between the type and severity of the associated heart disease and the rapidity of the response. In addition to the above-mentioned series of cases, the authors have treated several patients with paroxysmal auricular flutter and paroxysmal auricular fibrillation in an identical manner. In all, the rapid reduction in the ventricular rate occurred and frequently there took place a prompt reversion to normal sinus mechanism.

Tandowsky *et al.*,[83b] stating that they have failed to obtain consistent results by using digitalis leaf and quinidine, singly and in combination, for the abolition of auricular flutter, have studied the effect of the combined use of lanatoside C and quinidine in a series of cases. The glycoside was given intravenously in full digitalizing doses (1.6 mg.), with the effects being maintained by the administration of 1.0 mg. daily. Quinidine sulfate was used in varying doses, depending upon the individual requirements and tolerance (0.72 to 1.44 gm.). Following the intravenous administration of lanatoside C, frequent serial tracings were obtained. The authors have emphasized the necessity of continued lanatoside C therapy in maintenance dosage until auricular fibrillation makes its appearance. As soon as the conversion to auricular fibrillation took place, quinidine was given orally with

a maintenance dose of lanatoside C. Whereas quinidine was discontinued with the establishment of sinus mechanism, the prophylactic doses of lanatoside C were continued. This series included twenty-one patients, with the duration of auricular flutter prior to admission varying from three to twenty-eight days (the average pretherapeutic duration being approximately fifteen days). Three of the patients showed no evidence of heart disease. Twelve patients had received no specific therapy prior to admission. Four patients had full doses of digitalis, followed by maintenance doses of this drug for a number of weeks before the present study. Three patients received digitalis and quinidine and two had quinidine alone. None of these nine patients had been helped by the above-mentioned therapy. Following the intravenous administration of lanatoside C to this group of cases, a primary slowing of the ventricular rate occurred within one hour. (This particular effect on the ventricular rate, demonstrating an increase in A-V block, usually precedes the appearance of auricular fibrillation.) However, in four patients, this primary slowing of the ventricular rate was lacking. In four of the entire group, sinus mechanism was established without any medication other than the initial dose of lanatoside C. The time needed for this conversion varied from twenty to sixty minutes. Auricular fibrillation was established after the administration of lanatoside C in fifteen of the group in from two to seventy-two hours. In one patient, auricular flutter continued for thirteen days before auricular fibrillation was established. In another patient with thyrotoxicosis, the flutter remained unchanged. Quinidine sulfate was given orally to fifteen of those in whom auricular flutter was converted to auricular fibrillation. In addition, a maintenance dose of lanatoside C, consisting of 1.0 mg. daily, was given. While in one patient quinidine had been discontinued because of intolerance, in the remaining fourteen of this group auricular fibrillation was successfully converted to sinus rhythm over a period of twelve hours to ten days. The entire group of patients successfully restored to sinus mechanism were continued on a maintenance dose of lanatoside C, and were observed for periods from two to thirty-four months without a recurrence of auricular flutter.

In his book on heart disease, White[84] refers to lanatoside C as a ' reliable ' glycoside, and states that ' a very convenient and highly satisfactory way to digitalize rapidly is to use ampules of Cedilanid.' In the 1943 *Year Book of General Therapeutics*[85] the following editorial comment is found: ' It seems safe to predict that Lanatoside C will

replace all other preparations of digitalis for full digitalization in severe cardiac cases.' Most favorable reports are received from the Lahey Clinic, where the drug has been used rather extensively in the last two years. Rutledge[36] of the Clinic states 'we are impressed with its usefulness.'

Reports from European clinics disclose essentially the same information as reports in American literature. Michaud[37] confirms the rapid onset of digitalization and comparatively wide margin of safety. Objective improvement occurred two to four hours after intravenous administration and in forty-eight hours after the initial oral dose, six to eight tablets being given daily. Improvement of pulse and circulatory condition generally was accompanied by profuse diuresis.

Schildknecht[38] obtained excellent results with six to nine tablets daily (1.5 to 2.25 mg.). Full digitalization was achieved in forty-eight to seventy-two hours. After intravenous administration, the results were noticeable within a few hours. The author maintains that the heart effect persists for forty-eight hours after the drug is discontinued.

Pariscenti[39] reports distinct digitalis effect on the second day after taking six to eight tablets (1.5 to 2 mg.). He stresses the spectacular slowing of the ventricular rate in auricular fibrillation and adds that 'no untoward slowing occurs in cases of fibrillation with lower ventricular rate.' Other reports from abroad attest to the usefulness of lanatoside C 40, 41, 42, 43, 44, 45, 46, 47.

In our own experience with the drug in patients with congestive failure and auricular fibrillation or normal sinus rhythm, the therapeutic results have been most satisfactory on both oral and intravenous administration. The observations are similar to those reported by Sokolow and Chamberlain,[27,28] Fahr and La Due,[20] and others. Of the arrhythmias *per se*, auricular tachycardia, auricular fibrillation, and auricular flutter have been treated with lanatoside C. The results have been gratifying. Only very mild toxic reactions have occasionally been encountered.

A word of caution should be added. Whenever it is decided to produce rapid saturation with one large dose of cedilanid given intravenously, it is most important to ascertain how much digitalis the patient may already have had and how recently. This, of course, applies to any procedure of digitalization employing any one of the cardioactive principles, but is particularly vital in case of rapid saturation by the intravenous route. Intravenous administration of cardiac glycosides to patients who have taken digitalis within the preceding ten

days had been noted to be followed frequently by uncontrollable nausea and vomiting, premature auricular and ventricular contractions, pulsus bigeminus, ventricular tachycardia, ventricular fibrillation, heart block, and cardiac standstill.[48]

Ray and La Due[49] have decided to test the validity of the above-mentioned concept. They have aptly pointed out that there are no adequate means of determining definitely whether the patient with heart disease, associated with regular sinus rhythm, is receiving maximal therapeutic doses of digitalis. It has been deemed worthwhile to determine the toxic effects of the intravenous administration of cardiac glycosides (lanatoside C) to patients who developed congestive heart failure while taking maintenance doses of 0.1 to 0.3 gm. of digitalis leaf. In their previous study these authors discovered that the intravenous injection of lanatoside C to several patients who erroneously denied previous digitalization had not been followed by toxic manifestations. Hence, they decided that this problem was worthy of further study. They administered lanatoside C intravenously to sixty-two patients with congestive heart failure, despite the fact that they had been taking 0.1 to 0.3 gm. of folia digitalis daily for periods of weeks or months. Thirty-one patients were given 0.8 mg., twenty-two patients 1.2 mg., and nine patients 1.6 mg. of the drug intravenously. In this group of patients, thirteen had auricular fibrillation with apical pulse rates from 90 to 140, and forty-nine had congestive failure associated with regular sinus rhythm. All had venous pressures greater than 15 cm. of water on admission, and most of them had heart failure of a high degree. Maintenance doses of from 0.1 to 0.3 gm. of digitalis leaf were started six to twelve hours after the injection of cardiac glycosides. This regime was followed by definite improvement in forty-six of the sixty-two patients so treated. There was only one toxic reaction in the entire group. The mortality of patients studied was considered to be no greater than that previously observed in groups of patients with heart failure of comparable severity who had not been taking digitalis within three weeks prior to intravenous digitalization. It was felt that none of the deaths occurring during this investigation could be attributed to the intravenous medication. The authors concluded that the rate of improvement was more rapid than that to be expected from bed rest alone, and that, therefore, these patients were not receiving adequate theraputic amounts of digitalis. The tolerance of these patients to intravenous administration of lanatoside C was thought to be due to the need for more digitalis during the re-

currence of heart failure and to the possibilty that the destruction or elimination of the digitalis accumulated during the previous period of ' digitalization ' contributed to the onset of congestive failure. In spite of the favorable results described above, this author considers it wise to exercise caution in the intravenous administration of cardiac glycosides to patients who are known to have been receiving digitalis.

When compared with strophanthin, which lanatoside C approaches closely in effectiveness and rapidity of action on intravenous administration, certain advantages of cedilanid over the former drug become apparent. It is effective orally, as well as on parenteral administration, and thus the necessity of repeated injections is obviated for the maintenance of full therapeutic effect, after the state of emergency is no longer existent. Maintenance with oral doses is effected without changing to another preparation, as would be necessary in case of strophanthin preparations. The therapeutic/toxic ratio is more favorable in the case of lanatoside C. For a general practitioner, therefore, it may be a safer drug to use.

Summary and Conclusions

The perusal of literature and our own experience warrant the following conclusions in regard to lanatoside C:

The gravimetric method of standardization of lanatoside C obviates the need for bio-assay, which is an unsatisfactory method of determination of potency for cardio-active drugs. This constitutes a decided advantage over ordinary digitalis.

Lanatoside C is a stable, easily absorbed, and promptly effective preparation which can serve as a potent therapeutic agent.

Lanatoside C has all the indications of digitalis. It is thus most useful in congestive failure with either normal sinus rhythm or auricular fibrillation. It also has a field of application in certain types of cardiac arrhythmias (auricular fibrillation and flutter particularly).

Like any other cardio-active drug, crude or chemically pure, lanatoside C may exert toxic actions in excessive doses. However, due to the higher rate of elimination, the toxic symptoms are apt to develop less frequently than with cruder substances. Once these symptoms do appear, they subside more promptly for the same reason.

Intravenous preparations of lanatoside C are most satisfactory and reliable for use under circumstances when rapidity of action is indicated or oral administration for some reason is impossible or undesirable.

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CHAPTER IV

Other Cardiotonic Glycosides from Digitalis Plants

Digitaline Nativelle

In 1869 Nativelle[1] isolated from Digitalis purpurea a cardio-active principle, which was given the name of digitaline cristalisée. In 1875 Schmiedeberg[2] reported the isolation of a closely allied material, which he named digitoxin. Opinions vary about whether or not these two substances are the same. While Weese[3] refers to them as identical, Jacobs[4] believes that the two products are not exactly similar and states that digitoxin is the chief constituent of the original digitaline cristalisée of Nativelle. *New and Unofficial Remedies* uses the names digitaline cristalisée (Nativelle) and digitoxin interchangeably. Gold, Kwit, and Cattell[5] state that 'It is not possible to be certain as to whether or not Digitaline Nativelle and Digitoxin-Merck behave similarly in man.' Although it may not be possible to be absolutely certain about the identity of the materials of commerce called 'Digitoxin' and 'Digitaline Nativelle,' the credit for the initial isolation of digitoxin, the first discovered glycoside of digitalis, should probably go to Nativelle.

The empiric formula of digitaline Nativelle closely approximates $C_{41}H_{64}O_{13}$. It appears as thin, colorless, odorless crystals with a bitter taste and a melting point of 253 to 263° C. It is practically insoluble in acetone, chloroform, or ethyl alcohol. It is standardized by the intravenous cat method of Hatcher and Brody so that 0.42 mg. equals 1 cat unit. The preparations available are in the form of tablets containing 0.1 and 0.2 mg. of the active principle and 2 c.c. and 1 c.c. ampules containing 0.4 mg. and 0.2 mg. respectively.

Digitoxin has been shown by Hatcher[6] to be well absorbed from

the intestinal tract. This finding has been confirmed by other investigators.[7,8] Travel and Gold[9] have demonstrated in their experiments on cats that absorption is virtually complete. Animals in which vomiting was prevented by morphine frequently died in from two to six hours after an average intravenous fatal dose given orally. After larger oral doses (four to ten intravenous fatal doses), absorption was usually sufficient to cause death within less than an hour, even without morphine to prevent vomiting. These investigators concluded that the rapid onset of effect after oral administration might in part be due to rapid absorption of the glycoside directly from the stomach.

Extensive clinical studies were made by Gold, Kwit, and Cattell.[5] The authors set out to ascertain the doses of digitalis and digitaline Nativelle which would produce equivalent effects in the same individual. A group of forty-nine patients, some with auricular fibrillation and others with regular sinus rhythm, was selected. For the clinical assay of digitalis either the RS-T segment changes in the electrocardiogram in subjects with normal sinus rhythm or slowing of ventricular rate in those with auricular fibrillation were used as an 'end point.' While the authors found that in terms of equivalent weight digitaline Nativelle was about 200 times as potent as digitalis by the cat and frog method, the former drug was 1800 times as potent when the two were compared in man. It required from 6 to 12 cat units of digitalis leaf to produce the effects of 1 cat unit of digitaline Nativelle by oral administration. Complete digitalization by the latter drug was accomplished with the average of a total of 2.4 to 3 cat units (1 to 1.25 mg.). The authors advised dividing the full digitalizing dose into four or five fractions given during twenty-four to forty-eight hours. However, to one patient in advanced congestive failure with auricular fibrillation and a ventricular rate of 170 a minute, a full dose of 1.25 mg. was given at once; the results were 'quite dramatic.' The maintenance dose varied between 0.1 and 0.2 mg. daily. A daily dose of 0.2 mg. produced full digitalization in a week or two, and could be continued for many weeks. About one in ten patients was found by Gold and Kwit[10] ultimately to develop minor toxic effects with this dose. The toxic effects noted were similar to those following digitalis leaf: anorexia, nausea and vomiting, visual disturbances, dizziness, drowsiness, heart block, ventricular premature beats, bigeminal rhythm, and auricular fibrillation. The ratio of toxic to therapeutic potency was similar for digitalis leaf and the glycoside.

Lewis[11] recommends the daily maintenance doses of 0.25 mg. and

at most 0.5 mg. Stroud and Vander Veer[12] recommend 0.1 mg. as the daily maintenance dose and 1.2 to 2 mg. for full digitalization given over a period of five to six days. These are close to dosages advised by Gold, Kwit, and Cattell. However, while figures of Stroud and Vander Veer show that the cat unit of digitaline Nativelle is only four times as potent as the cat unit of digitalis in man, the former investigators have determined the ratio to be nine to one.

Gold, Kwit, Cattell, and Travel[13] have found the oral and intravenous full digitalizing doses to be practically identical, apparently due to the fact that the absorption of the glycoside from the gastro-intestinal tract in man is not far from being complete. In an extensive series of patients these investigators were able to determine that by employing digitaline Nativelle, the single full dose method of oral digitalization is effective and safe as a routine procedure. With this dose of 3 cat units (1.25 mg.) only one out of fifty patients develop nausea as a result of the local emetic action. The incidence of nausea from systemic action is similar. At the same time the authors found that a single average full digitalizing dose of digitalis produced sufficient gastro-intestinal disturbance to cause nausea and vomiting in one out of five patients within a period of minutes to less than two hours. This apparently is due to a local effect. Digitalization by a series of smaller oral doses of digitalis rarely causes symptoms due to a local emetic action. The high incidence of gastro-intestinal disturbance by local action after administration of digitalis leaf may be due to the fact that large amounts of the drug must be given because of incomplete absorption. The presence of impurities may also be a contributing factor.[13] The authors concluded that in contrast to digitalis, the use of digitoxin (digitaline Nativelle) in a single full oral dose ' provides a means of digitalizing a patient safely and rapidly within a few hours rather than in days, as is the case by the divided dose method in which digitalis is customarily used.'

Eichna and Taube[14] have administered successively lanatoside C, digoxin, digitaline Nativelle and ouabain intravenously to a patient in congestive failure with auricular fibrillation in equal gram-molecular amounts. They found that when compared, molecule for molecule, ouabain initiated effect most rapidly, and digitaline Nativelle most slowly. Between the two, but resembling ouabain more closely, were lanatoside C and digoxin.

In recent years additional reports on clinical evaluation of digitoxin have made their appearance. Thus, Katz and Wise[14a] have un-

dertaken a study to confirm the safety and comparative efficacy of folium digitalis and digitaline Nativelle in single digitalizing doses. Fifteen patients with chronic auricular fibrillaton were used in this study. These authors have attempted to evaluate the effects upon the resting heart rate of twelve oral administrations of 12.8 grains of U.S.P. XII digitalis leaf and twenty-four oral and two intravenous administrations of 1.2 mg. of digitoxin. The effects were similar, causing an average fall in heart rate of about 30 per cent in four to ten hours (average: seven hours). Digitalis leaf depressed the rate somewhat more than digitoxin, whereas the return to control level was more delayed, averaging eighteen days as compared to eleven days with digitaline Nativelle. This significant difference found in the time necessary for the heart rate to return to the pretreatment level range, and the tendency of the heart rate to retain a low level longer with digitalis than with the glycoside, appeared to indicate a more rapid excretion or destruction of the latter drug than of folium digitalis. The authors have concluded that either drug in the dosages used would appear to provide a safe, oral, single-dose digitalization, and might be useful when an effect is desired in a few hours. They have expressed their opinion to the effect that while single-dose digitalization was used experimentally, and frequently therapeutically, divided dosages, such as 0.8 mg. of digitaline Nativelle followed by 0.4 mg. in six to eight hours and by such subsequent doses as might be necessary to attain the desired results, would be preferable in most cases. The author of this monograph heartily agrees with their recommendations of more cautious administration of digitoxin.

Stewart and Newman,[14b] as a result of their clinical studies, have come to the conclusion that in most patients 1.2 mg. of digitoxin is insufficient for adequate digitalization when given either intravenously or orally. They have found the average dose to be around 2.0 mg., if given in twenty-four hours. It made no apparent difference in the total amount required within that period whether the drug is given in one single dose or in divided doses. The average maintenance amount of the drug was found to be between 0.1 and 0.2 mg., 0.2 mg. being too much for most patients. This recommendation for maintenance dosage is well taken, as instances of toxic effect after some months of maintenance on 0.2 mg. have been frequently coming to light in the recent years. With adequate digitalization, nausea and vomiting, in the experience of these authors, occurred more frequently with digitoxin than with the whole leaf.

There have been several reports on the toxicity of the drug. DeGraff and Batterman[14c] have compared three methods for the oral administration of digitoxin to produce initial digitalization in patients with congestive heart failure. Regardless of the method employed, an optimum dose was required for any specific patient before attaining a therapeutic response. The first method consisted in administration of an initial dose varying between 0.4 and 1.6 mg., with the greatest number of patients receiving 0.6 mg. Subsequent doses varied between 0.2 and 0.4 mg., with the greatest number of patients receiving 0.3 mg. In twenty-seven patients the therapeutic dose ranged from 0.7 to 4.08 mg., averaging 2.2 mg. The toxic dose ranged between 1.5 and 9.3 mg. (average: 4.1 mg.). The second method of slow digitalization by daily single doses was tried on patients who were not acutely ill, so that this procedure could be followed without jeopardizing their welfare. The daily dose in all but two cases was 0.4 mg. This dose was apparently selected because the authors, in their previous studies on the ambulatory patients, indicated this to be the minimal amount of the drug allowing sufficient cumulation for relatively rapid therapeutic response, while at the same time being sufficiently high to result eventually in minimal toxicity.[14d] The desired therapeutic response was attained in three to six days and required from 0.9 to 2.4 mg. (average: 1.7 mg.). It should be noted that this dose is slightly lower than that used with the first method; however, the two groups of patients are not comparable in terms of severity of congestive heart failure. The third method consisted of the administration of a single digitalizing dose of 1.2 mg. of digitoxin to a group of eighteen patients with chronic auricular fibrillation. Adequate digitalization was obtained by this procedure in only three patients (17 per cent). Since Gold and his associates had claimed that full digitalization is possible with a single dose, DeGraff and Batterman have made an effort to determine the exact level of digitalization attained. 'Titration' was achieved by administering a small dose of digitoxin at six-hour intervals, twenty-four hours after the initial dose, until a satisfactory therapeutic response was obtained and continuing until minor signs of toxicity occurred. Eleven patients required 0.4 to 3.3 mg. (average: 1.6 mg.) more than the initial 1.2 mg. to achieve a satisfactory response. The therapeutic dose in these patients ranged between 1.6 to 4.5 mg. (average: 2.7 mg.). An additional 0.9 to 6.9 mg. (average: 3.8 mg.) was required to achieve toxicity. The toxic dose varied between 2.1 and 7.1 mg. (average: 4.6 mg.). The authors have concluded that

digitoxin offers no particular advantage over digitalis leaf for the routine treatment of the patient with congestive failure. They have stated that: 'Because of its slow dissipation and the possibility of prolonged and severe toxicity, digitoxin is not in our opinion the glycoside of choice.'

Other reports of digitoxin toxicity have been made by a number of investigators. Master[14e] has reported nine cases of digitoxin poisoning and has concluded that 'digitoxin poisoning has now become so frequent in occurrence that it presents a real hazard.'

Flaxmann[14f] has pointed out that whereas over a period of fifteen years he had encountered digitalis poisoning infrequently, 'Late in 1946 and early 1947, when many switched to the isolated digitalis glycoside preparations, cases of digitoxin poisoning began to appear.' A total of thirty such patients have been seen by this author in a period of thirteen months. The toxic manifestations were mainly disorders of the cardiac mechanism, as twenty patients (66.6 per cent) had no symptoms. The other ten complained of anorexia, nausea, vomiting, weakness, and fatigue, symptoms that had not been present previous to the administration of digitoxin. The disorders of cardiac rhythm consisted in the appearance of premature contractions, auricular fibrillation, auriculoventricular block, sinus bradycardia, partial heart-block (P-R prolongation beyond 0.24 seconds), sinus arrest, and paroxysmal ventricular tachycardia. Two deaths occurred, one due to paroxysmal ventricular tachycardia and the other in a patient with auricular fibrillation and bigeminy.

Stone[14g] has recently reported a case of auricular tachycardia and auriculoventricular dissociation following the oral administration of 1.2 mg. of digitoxin in one dose. The patient weighed 125 pounds. Following elimination of some of the drug, the auricular tachycardia and auriculoventricular dissociation disappeared, but there still remained evidence of toxicity as demonstrated by the prolongation of the P-R interval to 0.28 seconds.

The author of this monograph has noted interesting neurological manifestations of digitoxin intoxication. An occasional patient would complain of tingling and numbness of the face and extremities, in addition to nausea or vomiting.

The evidence of digitoxin toxicity presented in the paragraphs above does not necessarily condemn the drug. The current clinical trials with this glycoside are reminiscent of the early period of strophanthin therapy. Owing to a lack of knowledge of what constituted

a safe dosage of the latter drug, many fatalities resulted from the employment of strophanthin in clinical practice. As a result, a very useful cardio-active principle fell temporarily into disrepute. However, with proper re-evaluation of the drug, it again came into prominence. It will continue to serve as a valuable therapeutic agent as long as the attending physician keeps in mind the close range between the therapeutic and the toxic doses of this glycoside. Since digitoxin has a definite cumulative action, the toxicity persists longer than that after other preparations. Hence, great caution is necessary in its administration. It must be remembered that while 1.2 mg. of digitoxin may be an average digitalizing dose, in many instances, particularly in patients of light weight, smaller amounts are indicated. On the other hand, in other patients more than the average amount must be used to achieve the desired results. Therefore, fractional doses, instead of a single full digitalizing one, are recommended. In addition, it must be remembered that the maintenance dose of 0.1 mg. may, when maintained for a long period, be a toxic one. Batterman and DeGraff[14d] have advised that digitoxin be made available in 0.05 mg. tablets. The daily maintenance dose of digitoxin probably varies from 0.05 to 0.2 mg.

Levine[14b] has made some pertinent remarks on the subject of digitoxin toxicity. The author has encountered development of arrhythmias in seven patients during a recent fifteen-and-a-half-month experience with digitoxin at the Peter Bent Brigham Hospital. Because these toxic effects appeared to be more frequent and insidious than with folia digitalis, he has undertaken a study of the incidence and manner of these toxic reactions in the group of patients mentioned above and in a comparable group that had received digitalis leaf. The arrhythmias observed were idioventricular rhythms, paroxysmal ventricular tachycardia, or interference and dissociation. These toxic rhythms are, of course, not peculiar to digitoxin. Five instances of toxicity of the type under discussion among 534 patients receiving digitalis leaf (0.9 per cent) compared with seven instances among 338 patients receiving digitoxin (2.0 per cent) did not present, in Levine's opinion, a significant difference, when the figures were subjected to statistical analysis by comparing the standard deviation of the difference with the actual one. He has concluded that: 'Hence, it cannot be stated as a positive fact that digitoxin has a greater tendency than digitalis to produce toxic reactions.' However, he concedes that with digitoxin cardiac arrhythmias may develop more insidiously than with the leaf. Thus, nausea and vomiting or diarrhea may not develop at

all to serve as warning signs of an impending more serious toxicity. This is probably attributable to the fact that digitoxin, by virtue of the relatively small effective dosage and its virtually complete absorption, has very little, if any, irritant effect upon the gastric mucosa, even when administered in a single full digitalizing dose. As a result, the attending physician is deprived of valuable warning symptoms that would demand withholding the drug. Therefore, it behooves anyone using digitoxin to be even more on the alert to the insidious development of other evidences of intoxication than with folia digitalis. Although these abnormal rhythms may be unpredictable and abrupt in their onset, they are frequently preceded by a rise in ventricular rate. The same effect may be produced also by the underlying disease process, and it may thus be difficult to evaluate the significance of such an increase in cardiac rate. Digitalis and cardiac glycosides frequently simulate by their toxic effects the same symptoms and signs that are the result of a failing heart. At any rate, the rise in ventricular rate in a patient treated with digitoxin should at least alert the physician to the possibility of a toxic effect. In addition, cardiac arrhythmias of toxic origin should be suspected whenever there is a sudden change from a totally irregular to a regular rhythm. This change may signify the establishment of an idioventricular rhythm with auriculoventricular dissociation.

Digoxin

In addition to the glycosides of digitoxin and gitoxin, in 1930 Smith[15] succeeded in isolating from Digitalis lanata an additional glycoside ' digoxin.' It will be recalled that digoxin is derived by hydrolytic cleavage from the natural glycoside lanatoside C of Digitalis lanata, and that it is formed by a chemical combination of a pentose sugar (digitoxose) with the cardioactive aglucone digoxigenin. It has been found to be a stable crystalline substance.

The pharmacological actions of digoxin have been investigated by White,[16] who has determined its toxicity in cats and frogs and has shown that it is cumulative in frogs, pigeons, and guinea-pigs. Comparative studies on toxicity in different experimental animals have been carried out by Walker.[17] These experiments have also demonstrated that the drug is cumulative. Demonstration by DeGraff and Lehman of a greater lethality of digoxin as compared with lanatoside C (in the cat) has already been mentioned. Wedd, Blair, and Dwyer[18] have demonstrated in animal experiments that the drug shortens systole,

both electrical and mechanical. Equal and rapid effect on the electrocardiogram by digoxin and lanatoside C has been shown by Eichna, Taube, and DeGraff.[19] Tandowsky, Anderson, and Vandeventer[20] described a depression of the RS-T segment and diminution of the T-wave amplitude on administration of the glycoside and comparing it with similar electrocardiographic effects of lanatoside C concluded that they were less marked in the case of the former drug. Evidence of digoxin effect was still apparent in eight hours following its exhibition.

The drug is promptly and fairly completely absorbed.[21] It can be standardized by weight. It is supplied in tablets of 0.25 mg. (1/240 gr.) and ampules for intravenous administration containing 1 and 1.5 mg. (1/60 and 1/40 gr.) of the active principle. About 0.2 mg. are equivalent to one cat unit.

Rose, Batterman, and DeGraff[22] have studied the clinical effects of digoxin on hospitalized and ambulatory patients. The ventricular rate in patients with auricular fibrillation was controlled, and diuresis occurred in the majority of the rapidly digitalized patients within twenty-four hours. The average therapeutic and toxic doses, as ascertained by rapid digitalization, were 3.75 mg. (19.5 cat units) and 6.0 mg. (31 cat units) respectively. The ratio of toxic to therapeutic doses was found to be similar to that of digitalis leaf. In the ambulatory group a considerably larger dose was required for maintenance than would have been expected from observations made on the hospital group of patients who were rapidly digitalized. This might have been due to the rapid elimination of digoxin noted by a number of investigators.[21,28] In their series of cases, Rose, Batterman, and DeGraff noted also other indications of rapid elimination of digoxin. Thus in the rapidly digitalized group of patients, toxicity was usually of brief duration. It usually disappeared within a few hours after discontinuance of the drug. In a few patients the toxicity produced by initial digitalization with digoxin subsided within twenty-four to forty-eight hours, even though an adequate daily maintenance dose of digitalis leaf was continued without interruption. This phenomenon is similar to that observed by Fahr and La Due in their experience with cedilanid (see chapter on Lanatoside C). The authors found digoxin rapidly effective when given parenterally. The therapeutic effect was frequently evident within fifteen minutes.

For rapid digitalization with the oral preparation, DeGraff and coworkers advise an initial dose of 1.5 mg. followed by doses of 0.75 mg.

at six-hour intervals until the desired therapeutic effect has been achieved. At this time a daily maintenance dose of 0.5 to 0.75 mg. can be given, and it may be decreased or increased by 0.25 mg. according to the requirements of each individual case. Contrary to the experience of some other investigators,[24] DeGraff *et al.* had no difficulty in establishing a maintenance dosage. For digitalization with single daily doses they advise 1.0 to 1.5 mg. The authors feel that digoxin satisfies the established criteria for a reliable, potent digitalis preparation.

Schwab[24] studied the effect of the drug in a group of patients with all types of organic cardiovascular disease. The criteria used for determining a satisfactory response were an increased urinary output, a fall in venous pressure, an increase in vital capacity, and a decrease in body weight. In patients with auricular fibrillation, the decrease in heart rate served as an index. The drug was given both orally and parenterally. The average single oral dose of 2 mg. was followed in six to eight hours by 0.5 mg. When used intravenously, the dose for the average adult was 1.5 mg. followed in six to eight hours by 0.5 mg. With this plan of dosage, the optimum effect was nearly always attained. A satisfactory therapeutic response was obtained in forty-four of the forty-eight patients studied. Of the remaining four, two subjects were moribund at the time the drug was administered and in the remaining two the therapeutic failure was also evident on exhibition of other cardio-active drugs. The author felt that the effects produced were ' comparable in all respects to those resulting from the use of the whole powdered leaf of Digitalis purpurea. The prompt amelioration of the distressing symptoms accompanying congestive heart failure was rather striking.' Schwab found that the effect becomes manifest earlier with digoxin than digitalis. In patients with auricular fibrillation, the slowing of the ventricular rate was apparent in one and one-half to two hours, reaching the maximum effect in eight to ten hours after oral administration. When administered intravenously the action is much more prompt, the effect becoming apparent within thirty minutes and reaching its maximum in three to five hours. The increase in urinary output following intravenous administration was noted in one to three hours, usually continuing for a period of twenty-four to forty-eight hours, depending on the degree of edema present. By the oral route, augmentation of urinary secretion became apparent in four to eight hours. Concomitant with cardiac slowing and onset of diuresis,

the venous pressure fell, the vital capacity gradually increased, and general subjective improvement ensued. In spite of the relatively large doses, toxic symptoms were comparatively rare. In the electrocardiogram, characteristic digitalis-like changes in the RS-T segments and T-waves were observed. The maintenance dose was found to vary between 0.5 and as much as 1.0 mg. The author felt that due to the relatively rapid elimination of digoxin, the maintenance of optimum effect is more difficult than with digitalis.

Eichna and Taube,[25] on administering digoxin intravenously to patients in congestive heart failure, noted rapid improvement in the circulatory dynamics. They found that the most striking and constant change was the rapid and considerable decrease in the elevated venous pressure (similar observations were made on using ouabain). This decrease occurred without change in ventricular rate when the cardiac mechanism was normal, but was usually, although not necessarily, accompanied by a slowing of the ventricular rate when auricular fibrillation was present. It was also found to precede the onset of diuresis. As there is considerable disagreement with regard to the change in cardiac output during restoration of circulatory compensation in patients with regular rhythm, the foregoing observations are of interest. Unfortunately no concomitant measurements of cardiac output were made by the authors.

Herrmann[21] found that full therapeutic effect would be achieved in most patients by administration of 1 to 1.5 mg. of digoxin. Intravenously the dose of 0.75 to 1 mg. was sufficient. The author states that in view of the rapid elimination of the glycoside from the body, the daily maintenance dose is about one-third of the full digitalizing dose, namely 0.5 mg. This is in agreement with the observations made by Schwab.[24] On the other hand, DeGraff and collaborators found that a smaller maintenance dose may be quite adequate.

Batterman and DeGraff[14d] have made comparative studies on digoxin, digitoxin, and lanatoside C. Their series included seventy-four ambulatory patients. The authors have concluded that: 'For reasons of safety in administration and satisfactory maintenance, digoxin is the glycoside of choice.'

Evans, Dick, and Evans,[25a] as a result of comparative studies on a number of cardiac glycosides, have come to the conclusion that: 'Digoxin and lanatoside C prove the best and digitaline Nativelle was scarcely less efficient.' They recommend as a single digitalizing dose

of digoxin 1.5 mg. of the drug with intravenous administration or 2.0 to 3.0 mg. orally. With these dosages they found effective digitalization to take place within a period of about two to four hours.

In England, digoxin is used more extensively than in this country. In the report of the Therapeutic Trials Committee of the Medical Research Council of the British Medical Association the following dosages are recommended: ' A single dose of 1.5 mg. should be given by mouth to an adult weighing 140 pounds or over. The dose should be 1 mg. to 1.25 mg. in lighter patients. After six hours further doses of 0.25 mg. should be given every six hours. One-half mg. a day is the average maintenance dose, best given in divided doses.'

Gitalin (Amorphous)

In 1912 Kraft[26] obtained a new substance from a cold-water extract of digitalis leaves. He gave it the name ' Gitalin ' and the drug was subsequently introduced into clinical practice under the name of ' Verodigen.' Gitalin is a glycosidal fraction of Digitalis purpurea. It is not to be confused with the chemically pure glycoside gitalin, which has an empiric formula of $C_{35}H_{56}O_{12}$ and occurs as white rosettes melting at 245° C. The commercial product gitalin, recognized in the *New and Nonofficial Remedies* is an amorphous substance and probably not a chemical individual. It is a yellowish-white amorphous powder, which is very soluble in chloroform and alcohol and in about 800 parts of cold water or salt solution. Amorphous gitalin of commerce begins to decompose about 110° C. and melts, though not sharply, at 150° C. In the dry state it has been shown to be quite stable, retaining its action without any change in potency or deterioration over periods as long as two years.

Straub and Krehl,[27] on the basis of their pharmacological studies, came to the conclusion that gitalin possesses all the properties common to the digitalis bodies. They demonstrated slowing of the pulse, increase in systolic contraction of the heart, and electrocardiographic changes. Mansfeld and Horn[28] used isolated frog hearts, weakened by perfusion with a solution containing one-half the proper concentration of calcium. These hearts were restored by the use of verodigen in a manner similar to that seen after the use of digitalis. The authors also presented in their paper an extensive review of the European reports dealing with pharmacological actions of the drug.

In this country Stroud, Vander Veer, and collaborators[29] have carried out some pharmacological studies with verodigen. On perfusion

of an isolated frog heart with the glycoside, the character of the effect produced was typical of digitalis action. The heart promptly showed a more powerful contraction, which was soon accompanied by a diminished relaxation. The improvement in contractions was more pronounced in hearts which had already become weakened. The diminished diastole gradually progressed until the systolic arrest. These investigators demonstrated some increase in cardiac output. The electrocardiographic records taken on dogs showed digitalis-like changes.

Good absorption of the glycoside from the gastro-intestinal tract has been demonstrated repeatedly.[27] Straub was of the opinion that the rate of elimination is such as to allow the optimum degree of accumulation. Stroud *et al.*[20] have shown prompt absorption in dogs.

With the frog assay method, verodigen has been found to possess 120 to 125 times the potency of standard digitalis leaves,[28,29] while with the cat assay method the corresponding figure is 130. European studies, both pharmacologic and clinical, tend to indicate that 0.8 mg. (1/80 gr.) of gitalin is equivalent to one cat unit of ordinary digitalis. The results obtained by American investigators have differed from these findings. While Stroud[29] found in the course of clinical observations this same amount of the drug (0.8 mg.) to be equivalent to three cat units when assayed on patients, Levy and Boas[30] concluded, on the basis of their clinical experience, that this quantity of gitalin (0.8 mg.), representing one cat unit biologically, was equivalent clinically to only two cat units. This only demonstrates again the fact mentioned in preceding chapters, namely that cardio-active principles may have the same potency by animal assay and yet one may be stronger or weaker than the other in man.

The drug is dispensed in tablet form, a tablet containing 1/80 gr. (0.8 mg.) of the gitalin powder, which is equivalent to 0.73 U.S.P. XII digitalis unit.

Stroud *et al.*[29] have made a clinical study of the therapeutic efficiency of verodigen on patients in congestive heart failure with regular rhythm and auricular fibrillation. The authors found that the drug controlled the ventricular rate well in cases of established auricular fibrillation and produced clinical improvement, with marked diuresis, in patients with congestive heart failure irrespective of rhythm. The electrocardiographic changes in RS-T intervals and T-waves were similar to those induced by digitalis. The total dosage necessary for optimum effect varied from 1/10 to 1/16 gr., administered over a period of five to six days. The most frequent adequate maintenance dose

was 1/240 gr. daily. Toxic effects from over-dosage were similar to those produced by digitalis. The authors caution that the potency of the drug demands ' careful observation in its administration, especially with patients who have recently been taking any digitalis preparation.'

Levy and Boas[30] have studied the action of gitalin on a group of ambulatory patients with auricular fibrillation. The average amount of gitalin which affected the ventricular slowing down to about eighty beats per minute was 7/80 gr. given in the course of two and one-half days. This agrees with the above-quoted observations of Stroud and his associates that clinical improvement and slowing of the ventricular rate in untreated patients with auricular fibrillation are affected by a total dosage of 1/16 to 1/10 gr. Rapid administration of gitalin produced prompt and effective slowing of ventricular rate and clinical improvement without the development of toxic symptoms. The daily maintenance dose of the drug was found to vary from as little as 1/240 gr. to as much as 1/40 gr., the average for the group being 1/110 gr. Of the patients who gave a statement relative to preference for either gitalin or digitalis, most had no preference, while the remainder gave as reasons for their preference for one or the other drug that they felt less tired, less dizzy, and less choked. Gitalin was found by the authors to have a persistence of action ' at least as long as digitalis.' The electrocardiographic changes were similar to those produced by digitalis. Toxic reactions to the glycosides were also the same as to digitalis. They were ' neither less nor more frequent.'

Baker and Bloom[31] also secured good results with verodigen, paralleling those obtained with digitalis. The quantity necessary for attaining full therapeutic response varied from 6/80 gr. to 10/80 gr., this closely corresponding to doses as determined by Stroud *et al.* and Levy and Boas. Herrmann[21] in his experience found that the optimal effect is accomplished by 1/16 gr. to 1/10 gr. administered in a period of five to six days.

Summary and Conclusions

Digitaline Nativelle, digoxin, and gitalin are useful cardiac drugs. Digitaline Nativelle has had a clinical trial in Europe and recently there has been renewed interest in the drug in this country. Because of its comparative purity, non-irritating nature, and good absorbability, this glycoside may be administered orally in full doses without producing gastro-intestinal irritation by local action. This allows at-

tainment of optimum therapeutic effect in a very short span of time, a condition which is difficult to achieve with oral digitalis leaf, as very large doses of the latter product are required – large enough to give rise to undesirable gastro-intestinal symptoms.

Digoxin also is an effective and dependable glycoside which can be used to good advantage. Gitalin also appears to be helpful.

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CHAPTER V

Strophanthus

THE active principle of Strophanthus is known by the general term strophanthin. There are many varieties of Strophanthus plant from which strophanthin can be obtained. Moreover, strophanthin is not a single substance of uniform chemical composition, but appears as a number of strophanthins, differing somewhat in chemical structure and pharmacological properties. No wonder the physician is confused when confronted by all these various products.

HISTORICAL DATA

Descandolle, a French botanist, was the first to describe the plant and gave it the name of Strophanthus because of the twisted shape of the flowers. The members of Livingstone's expedition to Africa became interested in the plant, which served as a source of arrow poison for the natives, and brought it to Europe. In 1865, Fagge and Stevenson[1] experimenting with this substance came to the conclusion that it was a heart poison, as on administering it to the frog they discovered that it stopped the heart. In 1872, Fraser[2] confirmed their findings. He recognized that the arrow poison under investigation was identical with the substance obtained from the seeds of the Strophanthus plant. In 1890 he introduced the method of obtaining strophanthin and described its chemical properties.[3] Popper[4] was the first to study the physiological effects of strophanthin administered intravenously. As time went on more species of Strophanthus were identified, yielding different active principles. In 1888 Arnaud[5] obtained a crystalline substance from the wood of a tree, Acocanthera Ouabaio, which was identical with strophanthin obtained from Strophanthus gratus, and gave it the name of Ouabain. The crystalline product from Strophanthus gratus

(g-strophanthin) was isolated by Thomas,[6] while Strophanthus kombé was found to be the source for another strophanthin known as k-strophanthin.

The active principles of this group of substances have been shown to be rather closely related to digitalis glycosides. The discovery of the cardio-active properties of these different products led to their introduction into clinical practice. Fraenkel deserves the credit of having established the rational form of therapy with strophanthin by a lifetime of effort. While attempts at cardiac therapy with the drug were made before, they were unsuccessful, due to oral administration. Fraenkel[7] in 1905–6 in Krehl's Clinic in Strassburg, after extensive pharmacological studies, for the first time treated cardiac patients systematically with strophanthin by intravenous injection. He obtained excellent results. The drug promptly became popular, but before long fell into disrepute because of a number of deaths. These accidents were the result of overdosage or disregard of previous digitalis therapy. However, the prejudice against the drug has prevailed unjustifiably ever since, and the reports of the fatal incidents have produced a lasting impression. Pick and Kisch, in this country, have stimulated interest in strophanthin and it may come into more widespread use for certain specific situations arising in practice.

Source and Chemical Structure

In the botanical group of the Apocynaceae, the various Strophanthus species, particularly, have been found to be rich in cardiac glycosides. The work of Jacobs and his associates contributed a great deal toward bringing order in the field of Strophanthus principles. They identified various members of the group and established their relationship with other cardiac glycosides.

Jacobs and Hoffman[8] found cymarin (k-strophanthin-α) to be an essential constituent of the mixture of glycosides present in the seeds of Strophanthus kombé. Its composition has been determined by Windaus and Hermanns,[9] who succeeded in obtaining it from various species of Apocyanum. In hydrolysis cymarin yields the aglucone strophanthidin and the methylated deoxysugar cymarose. The same species of Strophanthus has been demonstrated by Jacobs and Hoffman[8] to contain also a series of glycosides which are formed from cymarin by the addition of one or more molecules of glucose. Thus the glycoside (cymarin) with one additional glucose molecule becomes k-strophanthin-β. While the latter has been isolated in a crystalline state, the more

complex derivatives richer in glucose have been obtained as amorphous substances. At first it was thought that Strophanthus kombé contained only one crystalline principle k-strophanthin, but Jacobs has demonstrated that the latter actually represented a mixture of cymarin (k-strophanthin-α) and k-strophanthin-β (k-strophanthin-α + 1 molecule of glucose).

Recently, Stoll, Renz, and Kreis[10] reported the isolation of a new glycoside from Strophanthus kombé, k-strophanthoside, which differs from k-strophanthin-β only in containing one more molecule of glucose. As the sugar content of the compound increases, so does the pharmacological effectiveness, according to Rothlin.[11] Kisch,[12] who has had a wide experience in this field, states that k-strophanthoside is the most effective glycoside of Strophanthus kombé. It is marketed under the commercial name of Strophosid.

On the other hand Chen and collaborators[13] feel that the number of sugar molecules of a cardiac glycoside does not necessarily influence the degree of activity.

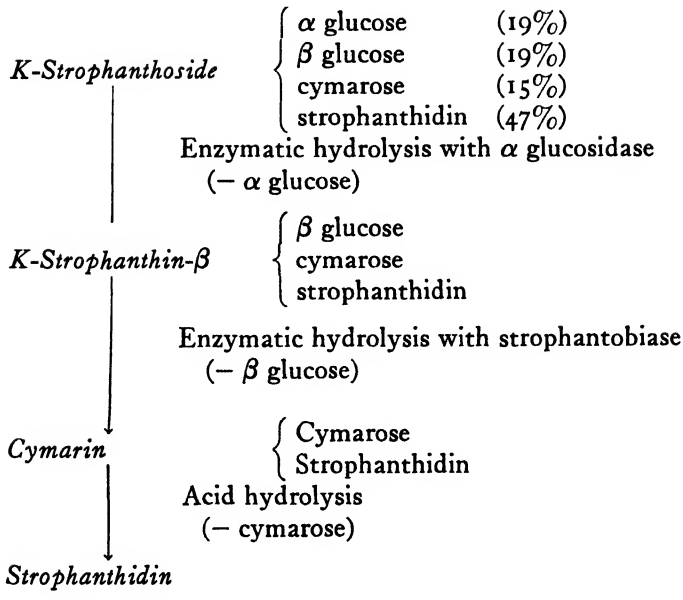
Jacobs found in the seeds of Strophanthus species an enzyme, strophanthobiase, which is characterized by its ability to remove glucose molecules from strophanthins. Thus, on enzymatic hydrolysis, the strophanthins richer in glucose may be reduced by successive steps of removal of one glucose molecule after another to glycoside cymarin (k-strophanthin-α), which contains no glucose. The effect of the enzyme stops there, but on acid hydrolysis cymarin further yields one molecule of methylated deoxysugar cymarose and one molecule of aglucone strophanthidin (the cardio-active principle).

According to Jacobs, strophanthidin is also the aglucone of Strophanthus hispidus. On enzymatic hydrolysis this mixture of glycosides also furnishes cymarin.

While Arnaud[5] detected the glycoside ouabain in the bark of the ouabaio tree, a species of Acocanthera, Strophanthus gratus has been found to contain an identical substance, the glycoside named g-strophanthin. Both ouabain and g-strophanthin, although obtained from different sources, yield on hydrolysis a molecule of sugar (rhamnose) and the aglucone ouabagenin (cardio-active principle).

From still another species of Strophanthus, S. sarmentosus, Jacobs obtained a complex preparation of glycosides, which on treatment with the enzyme strophanthobiase gave rise to a single glycoside sarmentocymarin. On further hydrolysis the latter yields a molecule of sugar sarmentose and a molecule of aglucone sarmentogenin.

TABLE VII



It appears that the species Strophanthus emini contains a mixture of glycosides similar to k-strophanthin. Bedford, Campbell, and Wood[14] called it strophanthin emini and proved its effectiveness clinically.

TABLE VIII

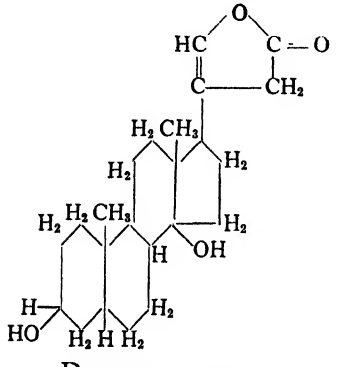
Source	Glycoside	Sugar	Aglucone
Apocynaceae			
Strophanthus			
S. sarmentosus	Sarmentocymarin	Sarmentose	Sarmentogenin
S. gratus	G-Strophanthin	Rhamnose	Ouabagenin
S. kombé	K-Strophanthin- K-Strophantoside	Glucose + cymarose Glucose (2 Mol.) + cymarose	Strophanthidin Strophanthidin
S. hispidus	Cymarin (K-Strophanthin-)	Cymarose	Strophanthidin
Acocanthera (ouabaio tree)	Ouabain	Rhamnose	Ouabagenin

The strophanthins generally used in clinical practice are those derived from Strophanthus gratus (g-strophanthin), Strophanthus kombé (k-strophanthin-β and k-strophanthoside), and the ouabaio

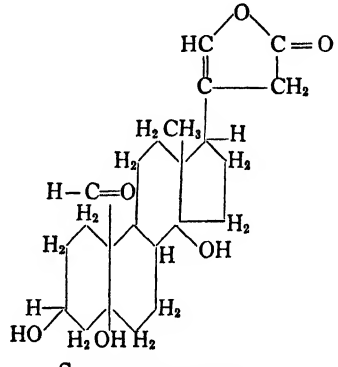
tree (ouabain, identical with g-strophanthin). Prepared from S. hispidus, h-strophanthin is also available commercially and is used in Germany.

The aglucones strophanthidin and ouabagenin are closely related to the aglucones of digitalis glycosides.

Strophanthidin	$C_{23}H_{32}O_6$
Ouabagenin	$C_{23}H_{34}O_8$
Digitoxigenin	$C_{23}H_{34}O_5$

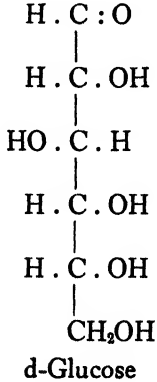


DIGITOXIGENIN

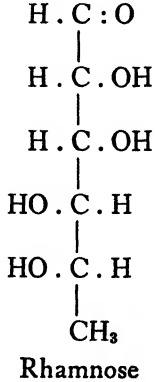


STROPHANTHIDIN

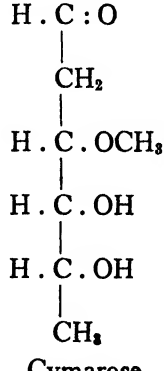
The sugars found in association with these aglucones in the glycoside moeity are found in nature only in cardiac glycosides, with the exception of glucose.



d-Glucose



Rhamnose



Cymarose

As in the case of all cardiac glycosides, cardio-active principles (aglucones) of strophanthins are less active than the corresponding glycosides. The addition of the sugar to aglucone enhances its activity.

Thus Chen and Elderfield[15] have demonstrated that aglucone strophanthidin is about ⅕ as active in frogs and ⅓ as active in cats as cymarin. On the other hand the same authors have demonstrated that oxidation of the aldehyde group on C_{10} of strophanthidin to form strophanthidinic acid is followed by substantial diminution of action, strophanthidinic acid being approximately 8 times less active in cats and 153 times less active in frogs, than strophanthidin. Saturation of the double bond in the side chain has been shown by the authors to be accompanied by practically complete loss of activity as exemplified by dihydrostrophanthidin, dihydrostrophanthidinic acid, and isostrophanthidin. 'Very marked reduction or often complete loss of activity may occur when stereochemical rearrangement in the steroid ring system has taken place as illustrated by pseudostrophanthidin, allocymarin and allostrophanthidin. These results indicate clearly that the digitalis-like action of strophanthidin and cymarin depends on not only a side chain with intact double bond and lactone ring but also the steroid ring system in favorable spatial isomerism.'

Pharmacology

From the discussion of the chemical structure of strophanthins it is quite apparent that digitalis and strophanthin are chemically related substances. However, although the aglucones are very similar, the structure of the sugars with which these aglucones are combined, is essentially different. While digitalis glycosides contain a methyl pentose, which is broken down in the human organism only with difficulty, the strophanthins contain mostly pentoses and hexoses which are easily broken down in the human body and are very readily soluble in water. This peculiarity of strophanthins may be the reason for their chemical properties being different from those of the digitalis glycosides. These differences are also reflected in their pharmacological actions.

The physiological effects of strophanthin have been confused with those of digitalis. Sir James Mackenzie[16] stated that he could not find in practice any difference between the actions of the two drugs. Strophanthin has been called a 'digitalis body.' Some investigators have used this term to imply an unqualified similarity between digitalis and strophanthin. It is true that the term is well justified in view of chemical, pharmacological, and therapeutic similarities of the two groups of cardio-active drugs. However, in the medical literature there can also be found observations and opinions in support of the view that the physiological properties of the two groups of drugs differ in certain respects.

Effect on the Circulation

Strophanthin increases the efficiency and hence the force of systolic contraction. The investigations of Wiggers and Stimson[17] and others have demonstrated that this is due to a direct action of the drug on the heart muscle independent of any nervous influence. While the force of systolic contraction is enhanced, the duration of systole shortens. As a result the diastole becomes longer as does the recovery period after every contraction. Clark and Mines[18] as early as 1913 demonstrated direct cardiac action of the drug on the excised hearts of frogs. This effect is particularly evident in a damaged heart, as demonstrated by Anitschkoff and Trendelenburg[19] and others. Weese[20,21] held that the drug was particularly effective in failure when the heart is hypertrophied. In toxic doses the effect of strophanthin on the myocardial contractility culminates in cardiac paralysis.[12]

The increase in force of systolic contraction of a failing heart increases cardiac output. Grassmann and Herzog[22] have demonstrated that in patients in congestive failure with diminished stroke volume and minute output, strophanthin increases the stroke volume and not infrequently the minute output as well. This effect becomes apparent in only a few minutes after the intravenous injection, and the increase may amount up to 50 per cent. As with digitalis, and probably by virtue of the same mechanism, in normal subject the administration of strophanthin in therapeutic doses may have an opposite effect, resulting in diminution of cardiac output. Tainter and Dock[23] have demonstrated on animals that this decrease results from peripheral action of the drug, manifested by constriction of the hepatic veins leading to diminution in venous return to the heart. Wegria[24] also found diminution in cardiac output in normal animals after injection of a relatively large dose (0.25 mg.) of ouabain, while similar results were obtained on normal human subjects by Gotsch.[25]

Strophanthin has been shown to slow down the conduction between the auricles and ventricles, as in the case of digitalis. This has been demonstrated in experimental animals and in human subjects. Clark and Mines[18] and more recently Reichel[26] and others have succeeded in producing with strophanthin in the frog's heart all degrees of A-V block, including complete auriculo-ventricular dissociation. The same results have been obtained with the mammalian heart by Sakai.[27] Although according to Auer[28] the drug does not prolong the A-V conduction time, the opinion is contrary to the experience of

most investigators, both in experimental and clinical fields. The ventricular slowing by strophanthin in cases of auricular fibrillation with rapid ventricular rate is to a great extent due to such action of the drug on the junctional tissue. On the other hand, the partial auriculoventricular block secondary to insufficient nourishment of the diseased heart muscle has been found by Kisch[29] to disappear on strophanthin therapy. The same effect of treatment with digitalis has already been mentioned.

This influence on conduction has been demonstrated to be due to the vagal effect as well as to direct action on the junctional tissue. As with digitalis, the latter effect is predominant with higher doses.[12] It has been shown on patients that A-V block appearing after injection of strophanthin may disappear on administration of atropine.[30] On the other hand Lewis, Drury, and Iliescue[31] have shown that the direct influence of strophanthin on the conduction system is also a factor of importance in production of A-V block.

It has been demonstrated in experimental animals (frogs and cats) by Gulik,[32] Krueger and Unna,[33] and others that strophanthin may slow cardiac rate by slowing the stimulus production in the sinus node. Domenighini and Grigolo[34] claim that the same effect is present in cardiac patients. The retarding effect on the stimulus production is believed to be the result of a twofold action: direct action on the sinus node, and the influence via the vagal nerve. The former effect has been demonstrated experimentally by Neter,[35] as it persisted after administration of atropine. The increased vagal effect is believed to be due to the combination of increased vagal tone and the increased sensitivity of the heart to vagal influences. The latter factor has been demonstrated by Kisch,[36] who applied blotting paper soaked in strophanthin solution to the region of the sinus node of the heart of animals, concurrently with artificial vagal stimulation. Kisch[12] is of the opinion that in intact animals and human subjects the increase in vagal tone is the predominant factor in slowing impulse production in the sinus node. When compensation is regained under the influence of strophanthin (or any other cardio-active principle) the decrease in intra-auricular pressure with relief of venous congestion slows down the heart reflexly, through the vagus nerve (Bainbridge reflex).

Coincident with the increase in efficiency of a failing heart leading to better emptying is the diminution in the diastolic volume of the heart. This has been shown both on experimental animals and cardiac patients. Mies[37] has demonstrated that in rabbits the cardiac dilatation

resulting on cutting the presso-receptor nerves receded more quickly on administration of strophanthin. The same effect on dilated heart has been found clinically.

The beneficial effects of strophanthin on the heart, as in the case of all other cardio-active principles, is dependent on certain changes of physio-chemical nature. Many of the latter have not been elucidated and are awaiting further investigation.

Gremels[38] has demonstrated that strophanthin diminishes oxygen consumption proportionate to the work done by the heart in failure. Gollwitzer-Meier and Krueger[39] have confirmed these findings of Gremels. The ratio of oxygen consumption to work performed by the failing heart is known to be increased as compared with the normal heart. In other words, the efficiency of the diseased organ is diminished. The glycoside decreases this ratio, bringing it closer to normal, and this change is reflected physiologically in enhancement of cardiac efficiency.

With improvement in cardiac efficiency the venous pressure falls (if elevated before strophanthin therapy) and venous congestion is relieved. Anitschkoff and Trendelenburg[10] have demonstrated in their work on heart-lung preparations the fall in venous pressure under the influence of the glycoside, but only when the heart is in failure. Villaret, St. Girons, and Lutin-Besançon[40] demonstrated the same effect of the drug in cardiac patients. At least in part this fall must be due to a decrease in circulating blood volume which is usually increased in failure. This decrease of blood volume by strophanthin has been demonstrated in cardiac patients by Mies.[37] At the same time the circulatory velocity is increased, as shown by Edmunds and Vogt.

While in normal people the blood pressure is believed by some investigators to remain unchanged,[22] the effect of the drug is different under conditions of failure. With restoration of compensation, the lowered blood pressure is raised to the level existent prior to failure.[25] Tainter and Dock[28,41] have shown that following the administration of strophanthin the arterial blood pressure increases, while the pressure in the right auricle falls. Experimentally, strophanthin appears to have a more striking effect on blood pressure than any other glycoside. Eichna and Taube[42] have demonstrated a prompt and transient rise in blood pressure in their studies on ouabain administered intravenously to patients with cardiac decompensation.

The results of investigations in regard to the effect of strophanthin on coronary circulation are contradictory. The results of animal experimentation are rather difficult to evaluate in terms of the possible

clinical effect in man. The flow through coronary vessels depends not only on their patency, but also on the mean arterial pressure, as well as other factors. Loeb,[43] on perfusing a cat's excised heart with stroplanthin, failed to find any appreciable change in the coronary flow. Bond[44] reported that strophanthin had no effect on the velocity of coronary flow in the intact cat. Similarly Gunn,[45] on perfusion of a rabbit's heart with a dilute solution of crystalline strophanthin, found little evidence of any constricting effect on the coronary vessels. Ginsberg, Stoland, and Silver,[46] carrying out their studies on heart-lung preparations in intact dogs, observed an initial reduction in coronary flow followed by longer lasting increase. Sakin[47] found in experiments with artificially perfused isolated hearts of rabbits that a solution of 0.0001 to 0.00005 per cent strophanthin in Locke's solution produces a constriction of the coronary arteries, while a solution of 0.00002 per cent cause a vasodilatation.

As to the effect of strophanthin on peripheral vessels, Tainter and Dock[41] have demonstrated in their experiments on dogs a rise in pressure in the portal vein after administration of the drug. On elimination of the liver from the circuit by means of an Eck's fistula these changes were no longer observed. On the basis of these findings the authors concluded that the rise in pressure in the portal system is brought about by constriction of the hepatic vein. The constriction of the hepatic vein would diminish the venous return to the heart and thus lead to decrease in cardiac output. Osterwald and Meurer[48] in their experiments on dogs came to the conclusion that in addition there can be demonstrated a diminished flow through the vessels of the extremities as well as in the splanchnic area. Beco[49] in his experiments on dogs concluded that ouabain has a constricting effect also on the vessels in the brain. The peripheral action of the drug is responsible for diminished cardiac output in normal subjects.

The diuretic effect of strophanthin can be explained on the same basis as in the case of digitalis. With a general fall in venous pressure, reabsorption of edema fluid results in the periphery and effective renal excretion is aided by relieving passive hyperemia of the viscera.

Gremels[50] and Hildebrandt[51] believe that cardiac glycosides may have direct effect on the vessels of the kidney, therapeutic doses dilating the vessels, particularly the vasa efferentia. Gremels[52] also believes that cardiac glycosides have a direct effect on the renal parenchyma; he found that the drug increases the oxygen consumption of the kidney in heart-lung preparations. Whether these extra-cardiac effects of digitalis and related bodies

play a significant role in promoting diuresis in cardiac patients is a question which has not been definitely settled. It has already been pointed out in the chapter on Digitalis folium that the general improvement in circulation is probably the most important factor.

It thus can be seen that generally the effects of strophanthin on failing circulation are similar to those of digitalis. When administered to patients in heart failure with auricular fibrillation or sinus rhythm, the glycoside strengthens ventricular contraction, increases cardiac output, decreases the diastolic size of the heart, relieves venous congestion, lowers venous pressure (if initially elevated), reduces circulating blood volume, and promotes diuresis.

However, some physiologists and clinicians are of the opinion that although the actions of strophanthins and digitalis are comparable they are not identical, inasmuch as different physiologic functions are influenced by the two groups of drugs in varying degrees. It is believed that strophanthin acts to a lesser extent on the sinus node and the junctional tissue than digitalis. As a result, the sinus tachycardia in the presence of heart failure may not be as markedly reduced by strophanthin even though the cardiac function improves. For the same reason, in auricular fibrillation the bradycardia produced by strophanthin is not as marked as that induced by digitalis. This constitutes an additional evidence against Luten's thesis that digitalis bodies cause ventricular slowing in cases with fibrillation of the auricles only by virtue of their effect on myocardial efficiency. Thus in cases where depression of the conducting system is the objective sought, digitalis is believed to be superior to strophanthin. At the same time the direct action of strophanthin glycosides on the myocardium represents the chief characteristic of their action, and in that respect they are thought to be more potent than digitalis. In other words, while digitalis seems to act powerfully on the vagal mechanism which causes retardation of A-V conduction and hence is more effective in auricular fibrillation with rapid pulse, strophanthin seems to slow the pulse and slow A-V conduction by improving the ventricular action and thus reflexly increasing vagal inhibition.

Hadorn and Frey[58] feel that the question whether strophanthin influences the electrocardiogram in precisely the same manner as digitalis has not yet been definitely settled. While Cohn and Levy[54] concluded that the effect of strophanthin on the T wave in man is not as marked as that of digitalis, Herles[55] noted typical T wave changes after administration of the drug. According to Kisch[12] the RS-T segment and T wave changes are less frequently encountered with strophanthin

than with digitalis. Macleod[56] found shortening of the Q-T interval (electrical systole) in the frog's heart, and similar electrocardiographic change has been found in humans after administration of the drug by Hadorn and Frey[53] and others.* Rothberger and Winterberg[57] reported changes in the form and direction of the P waves after administration of strophanthin.

Decherd and Ruskin[57a] have found in their experiments on the isolated rabbit heart that strophanthin (strophosid) causes a prolongation of the intraventricular conduction time, as evidenced by the widening of the QRS complex, the effect being greater with increasing doses of the drug. The hearts were perfused through coronary vessels by a cannula tied into the aorta. The effect in question was noted on injecting the drug into the rubber connection of the cannula in a dose averaging 0.006 mg./kilo of weight of the intact rabbit. This finding is similar to the well-known effect of quinidine on the intraventricular conduction, but is rather an unusual one for a digitalis principle.

Toxic Effects

The toxic effects are similar to those of digitalis. There is some evidence to the effect that strophanthins may differ somewhat in toxicity. Thus g-strophanthin (ouabain) is believed to be somewhat more toxic than k-strophanthin. For example, Hatcher and Brody[58] found the following toxic equivalents of the different glycosides in the cat:

g-strophanthin (ouabain)	0.1 mg.
k-strophanthin (Bohringer)	0.13 mg.
k-strophanthin (Merck)	0.17 mg.

Lendle and Schwezbrock[59] obtained somewhat similar results. In their experiments on guinea pigs the authors found that with intravenous administration the minimum lethal dose of g-strophanthin was 0.33 mg. per kg. and of k-strophanthin 0.42 mg. per kg. Fraenkel, the originator of the modern form of therapy with strophanthin, points out that such results of animal experimentation cannot be very well translated into terms of clinical experience. Kisch[12] adds that ' it is well to stress again that clinically both types of strophanthin are being extensively used in therapeutic doses with the best of clinical effects.'

Cattell and Gold[60] carried out some experiments with the view of relating the minimal therapeutic doses of ouabain, lanatoside C and digitoxin to their minimal fatal doses. The therapeutic effects were observed on the

* In isolated hearts of experimental animals a prolongation of the QT interval has been demonstrated.[56a] Whether or not it may also be found early in the course of gradual digitalization of humans has not yet been determined.

papillary muscle of the cat's heart while the toxic actions were determined by cat method assay. The fatal doses of ouabain, lanatoside C and digitoxin were found to be 1:3:4. In their later work, these investigators[61] have demonstrated the ratio of the therapeutic doses for the same glycosides to be 1:20:1. Thus ouabain and digitoxin were shown to have approximately the same ratio of effectiveness as compared with the toxic dose, and also the same ratio of effective intravenous dose for patients with auricular fibrillation to fatal dose for the cat.

The gastro-intestinal symptoms of toxicity are nausea, vomiting, and diarrhea. The possible mechanisms responsible for these manifestations have already been discussed with regard to digitalis toxicity.

Cardiac arrhythmias are a prominent feature of strophanthin intoxication. Kisch[12] has demonstrated in animal experiments on both direct application of strophanthin solution to the heart as well as with intravenous administration, the appearance of auricular, nodal, and ventricular extrasystoles with bigeminal and trigeminal rhythms, and auricular fibrillation. Rothberger and Winterberg,[57] in animal experiments, have produced auricular fibrillation on vagus stimulation after intravenous administration of the glycoside. Krueger and Unna[83] in their studies on anæsthetised cats found that while atropine delayed the occurrence of cardiac irregularities following ouabain until about seventy-five per cent of the fatal dose had been injected, atropinization did not influence significantly the occurrence of irregularities produced by digitoxin. The authors interpreted these results as evidence for a difference in the cardiac action between the two glycosides. They concluded that ouabain has an effect upon the vagus which can be suppressed by atropine, while the digitalis glycosides (digitoxin) do not exert this action, at least not to the same degree.

As with digitalis, supra-ventricular premature beats are less common than ventricular ones. Danielopolu[62] demonstrated in 1922 bigeminal rhythm and attacks of paroxysmal tachycardia in human subjects. Paroxysmal tachycardias of both supra-ventricular and ventricular origin have been demonstrated repeatedly. Ventricular fibrillation has been shown in animals. Parade[63] and other investigators are of the opinion that death in patients following strophanthin administration can be in every instance attributed to fibrillation of the ventricles. Kisch[12] has shown in animal experiments that various types of tachycardia 'may suddenly stop and produce an irreversible standstill of the heart, whereas in other cases, the tachycardia changes to a ventricular flutter or fibrillation.' On the other hand, if arrhythmias are secondary to the underlying heart disease present prior to strophanthin

therapy, they may disappear following administration of strophanthin, as they frequently do after exhibition of digitalis.

The production of auriculo-ventricular block by the glycoside has already been mentioned. Production of some degree of block in cases of auricular fibrillation can be considered as a therapeutic action.

The appearance of arrhythmia is a danger signal. Whenever the glycoside provokes cardiac irregularity the physician has to proceed with utmost caution. It can be mentioned in passing that more slowly acting agents may be less apt to produce irregularities, possibly because variations in distribution of the active principle in the tissue are less marked (Dock). All drugs affecting heart muscle should be given slowly on intravenous administration to minimize variations in concentration at the onset of injection, as well perfused areas may be profoundly affected and others very little. This is due to the more rapid rise and subsequent fall in concentration of the drug in the blood stream when the drug is administered by intravenous route, resulting in lesser concentrations of the agent in the poorly perfused regions of the heart muscle (see discussion on origin of irregularities in the chapter on Digitalis folium).

Like other cardiac glycosides, strophanthin in high doses may produce necrosis of the myocardium, as shown by Buchner,[64] Remé,[65] and others. These changes are an anatomical counterpart of the toxic effects as reflected in disturbance of function (arrhythmias).

Visual disturbances have also been reported as manifestation of strophanthin intoxication by Sprague, White and Kellogg.[66]

Absorption, Elimination and Cumulation

As strophanthin is rather ineffective when given orally and is therefore administered instead parenterally (rarely by rectum), the question of absorption from the gastro-intestinal tract need not be discussed. Strophanthins are very rapidly effective on intravenous administration, which makes this form of therapy particularly applicable in desperate cases where rapid digitalization is desired.

After intravenous injection the drug disappears rapidly from the blood stream. Weese found that most of the glycoside is absorbed by the striated muscle. Next come the liver and kidneys; the heart is last. This investigator found that the latter organ absorbs only about 9 per cent of the amount given. In heart-lung preparations it has been determined that the lungs do not take up the drug at all. Thus both the blood and the lungs do not store the drug ordinarily. However, some accumulation of the active principle in the blood stream may result

from administration of large quantities of the drug. The greatest amount is absorbed by the skeletal musculature because of the proportionately greater bulk in the body, as per unit weight this tissue fixes only about 5 per cent of the amount absorbed by the heart. The liver also absorbs less per unit weight, only about one-third of the drug taken up by the heart.[67]

Straub[68] believes that the action of strophanthin is independent of the total amount and depends entirely upon the concentration. Grünwald[69] is of the opinion that although the concentration is the prime factor when large quantities are used, the total amount is of importance when the dilutions are small and when small amounts are compared. It must be remembered that small amounts and low dilutions are employed in clinical medicine. Weese[70] holds that the amount of strophanthin fixed by the heart depends not only on the concentration of the drug in the blood stream, but also on the time during which the heart is exposed to the drug in the circulating blood. The conflicting views relating to the importance of concentration and total amount of the drug, bearing such an important consideration on clinical practice, have been reconciled by Levine,[71] who demonstrated on cats that the total amount required to produce a toxic effect is independent of the speed of administration. On the basis of this finding the author concludes that the time required to produce an effect on the heart varies inversely with the concentration of the glycoside. As the heart fixes only a small portion of the drug from the blood, with the use of concentrated solutions the total amount is not important, for the part removed by the heart does not appreciably alter the concentration, while when dilute solutions or small quantities are used, the amount taken up by the heart diminishes the remaining concentration appreciably.

The problems of fixation of strophanthin by the heart, and of its elimination and cumulation, bring up the question of the old classification by Straub[72] of all cardio-active drugs into two groups. The glycosides of the first order comprise true digitalis principles (Digitalis purpurea and Digitalis lanata). The group of the second order contains the glycosides of strophanthus seed, of scilla maritima, adonis vernalis, convalaria majalis, and others. According to the original view the glycosides of the first order (Digitalis purpurea and Digitalis lanata) are characterized by their power of fixation in the heart muscle (as well as in other organs), by their gradual effect which manifests itself rather slowly, and by their cumulative action, while the second group with strophanthin as its main representative, possesses a weaker fixation power and smaller cumulative effect. However, more recent investigations have demonstrated that this division does not hold true.

Thus, for example, lanatoside C derived from Digitalis lanata (group of the first order) has a strophanthin-like effect (group of the second order) in regard to rapidity of action and cumulation. It is believed, however, that strophanthin is fixed by the heart tissue not as avidly as the active principles of the ordinary digitalis.[12] Straub[73] held the view that a glycoside containing a terminal sugar which is not amenable to easy disintegration by the organism will exhibit the property of stronger fixation in the body. This may explain why strophanthins are not as strongly fixed by the myocardium (and other tissues) as some other glycosides.

It has been demonstrated by a number of investigators that cumulation of strophanthin is not as marked as that of digitalis glycosides. Heubner and Nyary,[74] on the basis of their animal experiments, have found Digitalis purpurea and its most active glycoside digitoxin as more highly cumulative than strophanthin. Lanatoside C (the most active glycoside of Digitalis lanata) was shown to occupy an intermediate position. Thus strophanthins exhibit the shortest persistence of effect, which is of some clinical disadvantage. However, there is no unanimity of opinion on this subject. Thus Li and Van Dyke[75] have found in their experiments on dogs that ouabain is more cumulative than digitoxin. Garcia and Goldman[76] have demonstrated that while k-strophanthin administered intravenously acts within a few minutes, it is almost wholly excreted within twenty-four hours. However, the degree of cumulation is sufficient to exert some persistency of action.[77] The latter is apparently of sufficient magnitude to be of clinical usefulness.

As in the case of other cardio-active principles, little is known about elimination of strophanthins from the human organism. Some of the glycoside may be eliminated through the kidneys and perhaps even a greater part through the gastro-intestinal tract. Lendle[78] believes that elimination of strophanthin takes place not via excretion of the aglucone split off from the entire glycoside moeity, but by the process of disintegration of the glycoside complex in the body.

Standardization and Preparations

The official strophanthin (Injectio Strophanthini U.S.P.) when assayed as directed possesses a potency per mg. equivalent to 0.5 mg. of U.S.P. Ouabain Reference Standard. It is a white or yellowish powder, stable in air, containing varying proportions of water which it does not lose entirely without decomposition. The official strophanthin, however, is not a chemical individual, but contains a mixture of

glycosides obtained from Strophanthus kombé. It can be separated into a crystalline and an amorphous fraction. The crystalline fraction is about twice as toxic as an amorphous portion, and consists of a mixture of two crystalline glycosides, k-strophanthin-α (cymarin) and k-strophanthin-β. The amorphous fraction consists of glycosides which are derived from cymarin by the addition of two or more molecules of glucose. One such product, k-strophanthoside, is less toxic, as all amorphous strophanthin glycosides are, than the crystalline products (cymarin or k-strophanthin-β). Kisch[12] considers k-strophanthoside the most effective glycoside obtained from Strophanthus kombé. It is marketed under the commercial name of Strophosid (Sandoz) in ampules of 1 cc. containing 0.5 mg. (1/125 gr.) and 0.25 mg. (1/250 gr.) of the active principle. Strophanthin-k is available in 1 cc. ampules containing the biological equivalent of approximately 0.37 mg. of U.S.P. strophanthin (Abbott).* Reference to biological standards is not necessary as strophanthins represent chemically pure substances which can therefore be standardized gravimetrically. Ouabain (g-strophanthin) is dispensed in 1 cc. ampules containing 0.25 mg. (1/250 gr.) or 0.5 mg. (1/125 gr.) of the active principle. There are also available 2 cc. ampules of ouabain containing 0.5 mg. (1/125 gr.). Ouabain is an official preparation (Injectio Ouabain, U.S.P.). For oral use there is available a N.F. preparation of strophanthus, which when assayed by the prescribed method possesses a potency per gram equivalent to not less than 55.0 mg. of Standard Ouabain U.S.P. XII (Tr. Strophanthus, N.F.). It is practically inert, as strophanthin by mouth is notoriously ineffective, requiring huge doses.

Holste[79] has found that aqueous solutions of k-strophanthin in ampules lose their effect sooner than do solutions of g-strophanthin (ouabain). Levy and Cullen[80] have demonstrated that even when protected from the influence of light the solution of k-strophanthin shows marked loss of potency within a year. At the same time, g-strophanthin retains its potency for a number of years. Kisch[12] points out that while this deterioration is partly due to enzymatic hydrolysis, some of it is caused by alkalinization due to contact of the fluid with glass (similar observations in regard to aqueous preparations of Digitalis purpurea have already been mentioned). Kisch cautions that the manufacturers should use only well selected types of glass.

* Strophanthin used by Fraenkel is of a concentration which deviates from that of the U.S.P. The former product, which has been used so extensively, has approximately twice the therapeutic effect and toxicity of that prescribed by the U.S.P. The Abbott Laboratories have recently prepared k-strophanthin with the titre which corresponds to that of Fraenkel's strophanthin (Braunbaum).

Methods of Administration

The oral administration of strophanthin (tincture of strophanthus) is notoriously unreliable. Absorption from the gastro-intestinal tract is rather insignificant as shown by the fact that the average optimum dose of k-strophanthin is as little as 1/150 to 1/200 of the oral dosage.[81] Dimitracoff[82] found that in dogs the toxic dose of ouabain (g-strophanthin) by mouth was about thirty times larger than by intravenous route. Pribram[83] maintains that rectal administration is effective. Groedel[84] and Kisch[81] are of the same opinion. Apparently in the rectum the drug undergoes but very slight chemical alteration.[81] The sublingual administration introduced by Cornwall[85] has not become very popular.

The subcutaneous injection of strophanthin is too irritating, and the degree and time of absorption are uncertain. The intramuscular injection is also rather painful. Castaigne[86] used the intraperitoneal route, but this method of administration remains unpopular for obvious reasons.

The intravenous injection of strophanthin as introduced by Fraenkel is the universal method of administration of this drug.

Clinical Applications

Fraenkel[7] was the pioneer of modern strophanthin therapy. Unfortunately, soon after the introduction by Fraenkel of the intravenous use of the glycoside, the drug promptly fell into disrepute, because of a number of fatalities. The memory of the fatal accidents which followed the introduction of strophanthin by Fraenkel in 1906 caused a widespread prejudice against the drug, and served for years and even until today as a serious obstacle to its clinical application. It is still held in disrepute by a number of prominent authorities, such as Sir Thomas Lewis[87] and others. Lewis does not mention intravenous strophanthin therapy at all and like most other clinicians, advises against oral administration.

It has been shown that most fatalities were due to the employment of large doses and to the disregarding of previous digitalization. As much as 1 mg. had been administered initially and even repeated several times daily. The initial large dose was frequently given in spite of rather heavy doses of digitalis which the patient might have had immediately preceding the beginning of treatment with strophanthin. No wonder that in many such cases the results proved disastrous. Since adoption of the smaller dosage and careful regard to any possible

previous digitalization, the results have been excellent in the hands of many clinicians, both in this country and abroad. While in Germany, the followers of the Fraenkel School have relied mostly on k-strophanthin, ouabain has been popularized by Vaquez in France.

As long as intravenous administration is the one mostly used and the one giving the best results, other routes of administration will be discussed only briefly.

In intravenous strophanthin therapy it is most important to use accurate dosages and watch the patient most closely during the entire course of therapy. This applies of course to all methods of digitalization with any cardio-active drug, but is particularly important in case of intravenous strophanthin therapy. In the words of Fraenkel,[88] 'In strophanthin therapy it is necessary to adhere to exact dosage, and to take careful records of the effect of each and every dose, just as in experiments with animals, and even if the treatment be continued for a long time. . . Such a procedure, being based on scientific method, raises strophanthin therapy to the level of controlled experiment, and furnishes at the same time a guarantee of its safety.'

The important principles of strophanthin therapy are: (1) Administration of accurate doses. (2) The glycoside may be utilized only with very special precautions if the patient has received, recently, some digitalis. Strophanthin should not be given to a patient who shows evidence of previous digitalization, for rapid additive effect may result with manifestation of grave toxic symptoms. (3) Close observation of the patient, particularly during the initial period of rapid digitalization with strophanthin. (4) Immediate cessation of strophanthin therapy with the first appearance of toxic action.

As with digitalis, heart failure constitutes the primary indication for strophanthin therapy. Again in the words of Fraenkel,[88] 'There is no degree and no phase of cardiac insufficiency from the beginning of the disease, often difficult to gauge, to the stage of extreme abnormality in the distribution of the blood along with its accompaniments, which does not respond to the intravenous administration of strophanthin. Only the compensated heart on the one hand or the dying heart on the other hand not yet responds or no longer responds to this treatment.' The drug is of particular value when rapid digitalization may be desirable. In addition to heart failure the drug may be successfully employed in certain cases of cardiac arrhythmia without failure, such as auricular flutter or fibrillation with rapid ventricular rate.

Fraenkel, who has had a wealth of clinical experience with this drug, was the first to note the rapid effect following the intravenous

administration of the glycoside. He noted that the effect would become apparent in a matter of a few minutes. In cases of severe decompensation he recommends an initial dose of 0.5 mg. to 0.75 mg. of k-strophanthin. The 0.75 mg. dose is divided into two consecutive doses of 0.5 mg. and 0.25 mg. respectively, on the same day, but at an interval of six hours. Otherwise, when the patient's condition is not as critical, only 0.3 mg. is advised for the first dose. In patients with recent myocardial infarction, a smaller initial dose of only 0.2 to 0.25 mg. is used. In patients with A-V block the latter dose is also advisable.

Wyckoff and Goldring[89] reported the results of 248 injections of ouabain to thirty-two patients. They would give the drug when digitalis had not been administered during the preceding two weeks. In patients with auricular fibrillation, slowing of the pulse after intravenous administration was noted within five to twenty minutes in about 50 per cent of the cases, and in practically all cases the therapeutic effect was obvious within fifteen to thirty minutes. In their studies 0.5 mg. of the drug was injected as a first dose. This was followed by 0.1 mg. every half hour until the onset of a clinical effect as measured by slowing of the cardiac rate. The total dose administered varied from 0.7 to 1.7 mg. Thus their dosages were decidedly higher than the ones employed in a previous study by Hatcher and Baily[90] in 1910, who emphasized the fact that not more than 0.5 mg. of ouabain should be given within a twenty-four hour period. Wyckoff and Goldring, however, state that they have not observed any unfavorable results. Good clinical results were also obtained in three patients, who were the only ones who showed a normal rhythm, and who received from 0.5 to 0.9 mg. of the drug. By the method of summation of doses the authors reached the conclusion that the effect was entirely dissipated in five days. The dosage employed by them is regarded as too high by some clinicians. Vaquez and Lutembacher[91] recommend the use of only 1 mg. of ouabain within the first forty-eight hours with the initial dose of 0.25 mg., which may be repeated at two-hour intervals.

Cohn and Levy[54] described the action of ouabain in man. They gave an initial dose of 0.1 to 0.5 mg. and a second dose of 0.3 to 0.5 mg. an hour later. White[92] recommends a dose of 0.25 mg. to 0.5 of ouabain (or k-strophanthin), ' never more,' in cases of ' overwhelming congestive heart failure.' He states that the dose may be repeated in twelve hours and then once every day or two in the doses from 0.125 mg. to 0.5 mg. as needed. He feels that an interval of forty-eight hours should be allowed before the drug is administered intravenously to

patients who have previously been on digitalis. Fishberg[98] recommends at the beginning of treatment a maximum dose of 0.5 mg. of ouabain, followed by injections of 0.1 mg. at one-hour intervals until in cases of auricular fibrillation the cardiac rate is slowed to less than 80 beats per minute. These recommendations are apparently based upon the work of Wyckoff and Goldring mentioned above.

Chavez,[94] who has had an extensive experience with ouabain, recommends one injection daily of 0.25 mg. in a series of six doses and more in accordance with individual tolerance and clinical improvement. He states that in thousands of patients treated over twenty years he has not observed one fatality which might be attributed to the drug. He considers the field of usefulness of this glycoside to comprise ' acute heart failure, paroxysmal nocturnal dyspnea and attacks of acute pulmonary edema in persons suffering from failure of the left ventricle.' He feels that in patients ' with failure of the left side of the heart, chronic coronary insufficiency, long established hypertension and complicated syphilitic aortitis,' ouabain finds its chief indications. He considers results in these cases superior to those of digitalis. On the other hand, basing his opinion on the belief that digitalis acts predominantly on the sinus node and the junctional tissue, Chavez states that in patients in congestive heart failure with pronounced sinus tachycardia and particularly with auricular fibrillation, digitalis instead of ouabain is the drug of choice. In rheumatic heart disease digitalis ' reigns supreme.'

Rykert and Hepburn[95] selected for their studies, with four exceptions, patients with auricular fibrillation. The authors judged the clinical effects on the basis of the same criterion as Wyckoff and Goldring, namely the slowing of the ventricles. However, they used k-strophanthin instead of ouabain, employing as a standard dose 0.65 mg. In many cases this dose was repeated in an hour. In a case of auricular flutter it was given three times at hourly intervals. They observed a definite reduction in cardiac rate in five to fifteen minutes. The maximum effect was noted in twenty minutes to an hour. They came to the conclusion that a large dose of strophanthin is safe intravenously (provided digitalis has not been administered recently) and that it can be repeated with safety in an hour if necessary. However, the authors suggest that the dose ' should not be repeated until the rate has reached a stationary level or has started to increase.'

Brams, Golden, Sanders, and Kaplan[96] studied the effects of continuous use of strophanthin in thirteen patients with cardiac failure: eleven patients with hypertensive heart disease and regular rhythm and

two patients with rheumatic heart disease and auricular fibrillation. All patients were in an advanced stage of congestive failure. The initial dose of strophanthin was usually 0.5 mg., either as a single dose or as two injections of 0.25 mg. each given at an interval of 12 hours. Occasionally, only one dose of 0.3 mg. was given the first day. Subsequent treatment consisted of daily injections of 0.3 mg. There was marked clinical improvement in every instance. In only one case were any significant changes noted in the electrocardiogram (prolongation of the PR interval). The authors concluded that strophanthin is ' an ideal drug in acute cardiac emergencies such as paroxysmal dyspnea, cardiac asthma, acute pulmonary edema of cardiac origin or abrupt congestive failure.' They felt that it is wise to allow an interval of five days to elapse before administering strophanthin to a patient who has been previously well digitalized. They advise caution in cases of premature contractions, recommending in such instances smaller doses of 0.3 mg. to 0.25 mg. instead of the usual 0.5 mg. Continued daily injections of 0.3 mg. for as long as twenty-four consecutive days failed to produce significant clinical or electrocardiographic evidence of toxicity.

Grunbaum[97] recommends dividing the initial dose of 0.5 mg. of strophanthin given within the first twenty-four hours in two equal portions, administered within an interval of from eight to twelve hours. He considers a period of forty-eight hours as sufficient between cessation of digitalis therapy and the introduction of intravenous treatment with strophanthin. However, he feels that this period should be prolonged to at least seventy-two hours if rather large doses of digitalis (0.3 gram daily) have been taken. Pick[98] is of the opinion that if it is necessary to use strophanthin in a patient who has had digitalis and a rest of two or three days cannot be observed, small doses of strophanthin, 0.15 mg., may be injected very slowly, ' while careful watch is kept for the occurrence of extrasystoles,' as these are indications of strophanthin intolerance. Horst[99] advises smaller doses of 0.2 to 0.3 mg. of strophanthin daily (and in exceptional cases 0.35 mg.).

Scherf and Boyd[100] recommend a minimum period of three days after the cessation of digitalis therapy before strophanthin is administered. The authors do not advise an amount of strophanthin or ouabain exceeding 0.25 mg. per injection. In patients who have not received digitalis prior to institution of strophanthin therapy, two such injections daily can be given for the first few days.

Kisch,[12] stating that ' by no means should the patient undergo any risk from strophanthin treatment,' advises that the first dose administered, therefore, always should be as low as 0.15 to 0.2 mg. Thus pa-

tients whose reaction to strophanthin is unknown are carefully tested. ' This is especially important in desperate cases where the physician should never be misled into giving a high dose on account of the severity of the condition present. In the beginning such a patient needs a low dose.' This investigator has had considerable success on administering 500 cc. of glucose solution with 0.20 mg. to 0.25 mg. of the drug as a drop-infusion over a period of one to three hours. He feels, with many other clinicians, that the slower the injection the more beneficial it will be. Using an infusion in glucose solution, the difficulty of administering strophanthin slowly is lessened. The advisability of this practice of slow administration is based on the work of Weese[70] demonstrating that the amount of the glycoside fixed by the heart depends not only on the concentration of the drug in the blood stream, but also on the time during which the heart is exposed to the drug in the circulating blood. Kisch has observed excellent progress in patients to whom daily doses of 0.3 to 0.4 mg. have been administered. He states that a dose of 0.3 mg. daily can be given intravenously for weeks or months without risking toxic cumulative effects, because of the rapid elimination of the drug. He feels that doses of 0.6 mg. are rarely necessary and should not be overstepped except under special circumstances, when the smaller dose is not producing a desired result. He advised against administering strophanthin before twenty-four to thirty-six hours have elapsed following the last dose of digitalis. At the same time, however, Kisch quotes Fraenkel as not being adverse to eliminating this interval altogether, provided the initial dose of strophanthin is very small, about 0.15 mg.[29] He also points out that, as in the case of every cardio-active principle, there can be no rule of thumb for dosage, the latter requiring an individual selection in each case. It is felt by some that only the degree of decompensation indicates the size of the dose of strophanthin and that body weight can be disregarded. Thus Grunbaum[97] believes that body weight plays a part only when the toxic limit is approached, ' and then only when there are very great weight differences such as exist between the child and adult.'

Although Kisch states that for intramuscular administration the doses are similar to those employed intravenously, others[101] believe that intramuscular use requires higher dosages because some of the drug is fixed by the muscle with which it comes in contact. (There are special preparations available for intramuscular injections.)

When resorting to rectal administration, as much as 1/50 gr. of

strophanthin can be safely and effectively administered, one to three times daily.[12] Both intramuscular and rectal routes are employed infrequently.

In cases of recent coronary infarction one has to proceed with greater caution when the need for digitalization arises, as in the case of any other cardio-active drug. Uhlmann[102] believes that strophanthin should not be used during the first stormy days following infarction, but concedes that when dire need for such arises, 'injection of strophanthin may be life-saving.' Grunbaum,[97] Edens,[108] and others express the same opinion. Kisch[12] never begins with doses higher than 0.15 mg. in cases with angina pectoris or myocardial infarction, later increasing the dose to 0.2 mg. He states that if necessary these doses can be given twice daily. On the other hand, in toxic conditions, thyrotoxicosis, etc., higher doses are required. The existence of heart block is not a counter-indication to strophanthin therapy any more than it is to administration of digitalis, although in every such case, regardless of the drug employed, greater caution with employment of smaller doses is indicated.

After compensation has been regained, the full therapeutic effect apparently can be maintained over prolonged periods of time with repeated administrations of the glycoside. The dose and the frequency of injection will, of course, depend on the clinical condition of the individual patient, his reaction to the initial treatment, and his tendency to show even initial signs of recurrence. However, such practice has several disadvantages. It involves the employment of continued intravenous therapy, a procedure not too pleasant to the patient. It incurs an additional cost and creates an unwarranted degree of dependence of the patient on his doctor. Once the state of emergency has passed, there is no reason for continuing intravenous treatment, as maintenance of a full therapeutic effect can be produced by oral administration of cardio-active principles effective by mouth. Several such schemes have been proposed by different clinicians.

Although the action of strophanthin is rapid it possesses the disadvantage of quick elimination. As it is not known just how much of the glycoside remains in the body twenty-four hours after the administration, the dose of digitalis which is necessary to maintain the desired effect may be difficult to ascertain. Batterman, Rose, and DeGraff[104] have attempted to supplement and maintain the early action of ouabain by the simultaneous administration of a single dose of digitalis. The principle employed was that of obtaining quickly a de-

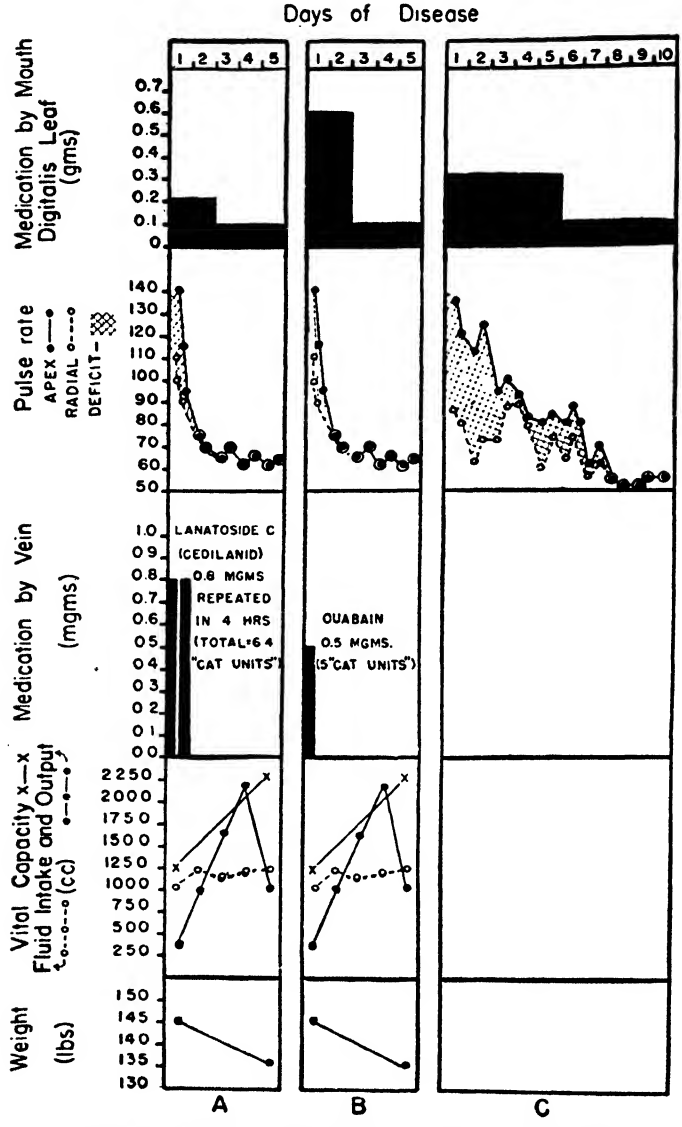


FIG. 16. Charts showing the effects of digitalis, lanatoside C, and ouabain in congestive failure and auricular fibrillation with particular reference to heart rate, clearing of pulse deficit (shown by shading above), fluid balance, vital capacity, and weight. A. Rapid effect during the first day of treatment by means of lanatoside C given intravenously followed by powdered digitalis leaf by mouth. The dosage is indicated on the chart. B. To illustrate essentially the same results to be expected by the use of ouabain intravenously followed by digitalizing dosage of powdered leaf by mouth. C. Slower but effective digitalization in a case of auricular fibrillation without congestive failure by powdered digitalis leaf by mouth. Dosage indicated on the chart. (From P. D. White, *Heart Disease*, 3rd Edition, 1944. By permission of The Macmillan Company.)

sired therapeutic effect with a rapidly acting drug and thereafter maintaining it with a drug (whole-leaf digitalis) which is more slowly absorbed and excreted. It could be expected that at the time when the therapeutic effect of ouabain passed its maximum and started to diminish, the slowly increasing action of digitalis would become manifest. A series of fifty-nine patients with varying degrees of congestive heart failure and different types of heart disease with normal sinus rhythm and auricular fibrillation, ranging in age from twenty-eight to seventy-nine years, were selected. 0.5 mg. of ouabain was given intravenously simultaneously with 6 or 8 cat units of digitalis orally; the amount of the latter depended on the estimated edema-free weight of the patient. No other digitalis was given for twenty-four hours. At the end of this time the patient was placed on a daily maintenance dose of 1 or 2 cat units of digitalis leaf by mouth. In the majority of cases, improvement occurred within one hour, and once established, was progressive, reaching the maximum at the end of a twenty-four-hour period. After the initial digitalization it was not difficult to establish the maintenance dose of digitalis. The authors found that 'evidences of toxicity were the least that could be expected, indicating that the method is a safe one.' Good results were obtained irrespective of cardiac rhythm. Thus, with this method of therapy, while the use of the glycoside (ouabain) brings about rapid improvement, the simultaneous administration of the more slowly absorbed digitalis not only maintains this improvement, but also decreases or abolishes the gap between the beginning of digitalization and the establishment of a maintenance dose.

Using the method of treatment outlined above on patients with congestive heart failure and chronic auricular fibrillation, Batterman and Engstrom[105] have determined the persistence of effect of the two drugs. The slowing of ventricular rate and improvement in myocardial efficiency in general, as manifested by relief from symptoms and signs of congestive failure, served as criteria for these determinations. The authors found that the duration of effect of ouabain and digitalis in combination was intermediate between that of ouabain alone and that of digitalis alone. Thus ouabain maintained a slow ventricular rate for a mean period of 4.3 days, ouabain and digitalis, for 9.6 days, and digitalis alone for 16.1 days. Considering the reappearance of congestive failure, the action of ouabain was found to persist on the average for 4.9 days, of ouabain and digitalis combined for 10.5 days, and of digitalis alone, 17.2 days. Thus, as might be expected, the persistence of effect upon the ventricular rate and control of congestive heart failure

were shortest after digitalization with ouabain alone, longer with ouabain and digitalis combined, and longest with digitalis alone.

Smith[106] used a procedure somewhat similar to that of Batterman and his co-workers on forty-six patients. Each patient was given 0.5 mg. of ouabain in 10 cc. of 10 per cent dextrose solution intravenously. Shortly after, four cat units of digitalis were administered. The maintenance dose of digitalis, usually one cat unit, was started during the second twenty-four-hour period. The improvement was rapid in every case and it continued until the digitalis effect appeared. Equally satisfactory results were obtained in patients with regular rhythm and auricular fibrillation. The toxic effects were minimal.

Gefter and Leaman[107] employed a similar procedure in thirty-three cases of rapid cardiac arrhythmias, with the ventricular rates ranging between 140 and 210 a minute (paroxysmal auricular tachycardia, auricular flutter, auricular fibrillation, simple tachycardia, and one case of ventricular tachycardia). While the patients were given the same 0.5 mg. dose of ouabain intravenously, the oral dose of digitalis leaf (4 to 8 cat units), however, was usually given approximately one hour following ouabain rather than simultaneously, in order to observe the effect of ouabain *per se*. In no case was ouabain used if the patient had taken digitalis during the preceding week. The cardiac rate was determined every five minutes for one hour, then at two, twelve, and twenty-four hour intervals. Electrocardiograms were taken at varying intervals following use of the glycoside. Although symptomatic improvement usually preceded objective evidence of improvement (sometimes being apparent within five minutes after injection of ouabain) a cardiac rate of 110 or less was arbitrarily selected as the time of optimum effect. Ouabain produced such an optimum immediate effect in one hour in 44 to 83 per cent of all heart disease cases except in the one case of congenital heart disease and in two cases without known organic lesion.* Fifty-seven per cent were improved in one hour, 63 per cent in two hours, and 85 per cent in twelve hours. Toxic effects were very few. Normal rhythm returned in seven of the twenty-four cases of auricular fibrillation within forty-eight hours. The authors concluded that one intravenous dose of ouabain produces a significant reduction in ventricular rate and is, therefore, an effective method of treating rapid cardiac arrhythmias of supra-ventricular origin. It was relatively ineffective in sinus tachycardia and in the pres-

* The excellent response in the case of paroxysmal ventricular tachycardia is difficult to interpret.

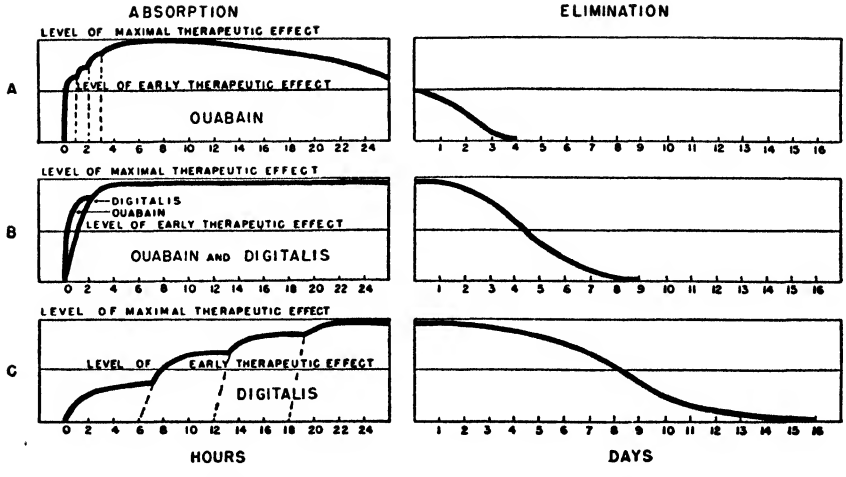


FIG. 17. Schematic representation of absorption and elimination of digitalis and ouabain: A. Of ouabain given intravenously by the method of Wyckoff and Goldring; B. Digitalis and ouabain in combination by the method of Batterman, Rose, and DeGraff; C. Digitalis leaf given orally by the method of Eggleston. By elimination is meant the persistence of digitalis effect upon the ventricular rate of patients with auricular fibrillation. (From R. C. Batterman, A. Rose, and A. C. DeGraff, *Am. Heart J.*, vol. 20, 1940.)

ence of infection. They felt that when combined with one oral dose of digitalis, intravenous ouabain is an effective aid in producing full digitalization.

Following the lead of Batterman *et al.*, Garcia and Goldman[76] treated a number of patients by this combined method of therapy, substituting k-strophanthin for ouabain. The cases selected for study included patients with acute and chronic heart failure, irrespective of cause, who had not previously received digitalis for a period of at least ten days. There were six cases of coronary arterial disease, three of hypertensive heart disease, five of combined hypertensive and coronary arterial disease, three of syphilitic heart disease, and one of thyrotoxic heart disease. The patients were given intravenously 0.25 mg. of k-strophanthin, diluted with 10 cc. of physiologic saline, over a period of three minutes. Immediately, six to nine grains of digitalis leaf were given orally, followed by three grains three times a day until the patients were digitalized. The criteria of recovery from heart failure consisted of disappearance of dyspnea, râles, cyanosis, and edema, diminution in the size of the liver, and return of the venous pressure to normal. Electrocardiograms were taken daily. The total amount of k-strophanthin given to each patient was 0.25 mg. The total amount

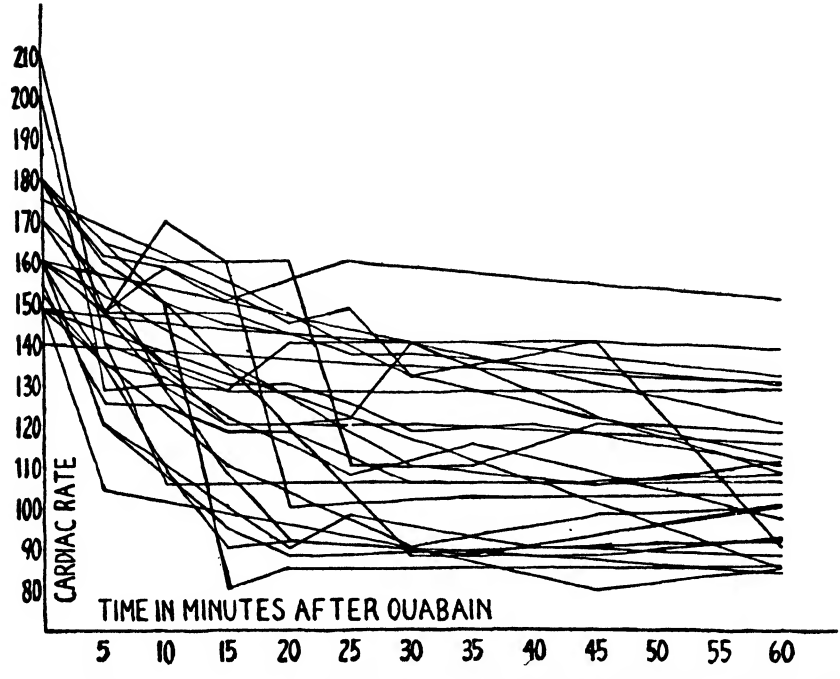


FIG. 18. Reduction in cardiac rate after ouabain treatment. (From W. J. Gefter and W. G. Leaman, *Am. J. Med. Sci.*, vol. 205, 1943.)

of digitalis required for digitalizing each patient ranged from 12 to 24 cat units, averaging 18.5 cat units. The average time required for the right side of the heart to compensate was 3.1 days and for complete compensation, 5.5 days. All patients noticed subjective improvement within the first two to six hours. This was progressive, and closely paralleled objective signs of improved cardiac function. There were practically no untoward toxic manifestations. Nausea and occasional vomiting occurred in some patients with full digitalization. Electrocardiograms failed to show any detrimental effect on the conduction mechanism. The heart rate was not strikingly altered during the first six to twelve hours, although there was a uniform and progressive slowing. In all cases of sinus rhythm, the latter remained unaltered. Of six patients with auricular fibrillation, in one there was a reversal to sinus rhythm; in this patient the arrhythmia has been present for two months, and followed thyroidectomy. The authors suggest that the absence of definite and more immediate bradycardia after the administration of strophanthin may be an indication for the possible necessity of giving a larger initial dose of the glycoside. They feel that clinical observa-

tions demonstrated the effectiveness of the combined use of strophanthin and digitalis, and that full digitalization after giving strophanthin played a major role in effecting this rapid result.

Kisch[12] does not see any objections to using such methods of combined therapy, as long as digitalis treatment follows and not precedes the administration of strophanthin.

Pertierra and Samia[107a] have treated a number of patients in congestive failure with k-strophanthoside (strophosid). They have reported ' remarkable, not to say dramatic, results.'

In recent years esters of strophanthidin have been studied pharmacologically by Chen and co-workers. It has been found that more potent derivatives than strophanthidin could be prepared, and that 3-acetyl strophanthidin (identical with strophanthidin-3-acetate) was the most potent of the entire series. In addition, in order to explore the changes of cardiac activity resulting from substitution in a single ester, several new derivatives of 3-acetyl strophanthidin have been synthesized. These derivatives have been studied pharmacologically in cats by Welles, Anderson, and Chen.[107b] The authors have found none of the new compounds to be as active as 3-acetyl strophanthidin. This work contains some references to the significance of certain structural changes in relation to cardiac activity of the compounds in question.

Gold *et al.*[107c] have studied the behavior of several synthetic esters of strophanthidin in man. They observed that these compounds, after intravenous injection, produced full effects very rapidly, within ten to thirty minutes. The persistence of action was very brief, the effects wearing off within a few hours. The authors thought that the typical digitalis action exerted by these materials, with the rapid onset and disappearance of the specific effect, ' provided a combination of characteristics with useful therapeutic possibilities.'

In a recent study by Gold and his associates,[107d] the action of strophanthidin-3-acetate has been compared with that of ouabain. Both compounds were administered intravenously to patients in heart failure accompanied by auricular fibrillation. The authors have found that strophanthidin-3-acetate exerts a more rapid action in man than any other digitalis material in common use, including ouabain. The full effect of the strophanthidin ester, injected intravenously, develops in a period from ten to fifteen minutes, and the effect wears off in a period of about four hours, as compared with ouabain, in which case an hour elapses before the effect develops and about thirty-six hours before it disappears. The authors have suggested the possible utility of strophanthidin-3-acetate in extremely urgent cases of acute failure with pulmonary edema, and for the purpose of terminating a paroxysm of auricular tachycardia or auricular flutter.

Summary and Conclusions

It has been shown conclusively that in experienced hands strophanthin therapy is productive of excellent results. Its particular value lies in the treatment of congestive heart failure when rapid digitalization is desired. Ouabain and k-strophanthin are well known and widely used. The more recently available k-strophanthoside may be even more uniformly reliable in cardiac emergencies.

As with other emergency treatment, strophanthin is best given intravenously. It is not suitable for oral or even intramuscular use. The effect of a dose does not reach its peak in less than one hour, but serious arrhythmias, or more rarely nausea, may be observed within a few minutes after the administration of excessive doses or therapeutic doses when the patient is still under the influence of digitalis given within a week or less. One does not wait for digitalis to wear off before giving strophanthin, since it would be simpler to give divided doses of digitalis at once (with not more than one-fifth of a full dose on initial administration). However, one may safely give 0.1 mg. of strophanthin every hour to patients in urgent need of a cardiotonic agent, and particularly in case of auricular fibrillation with ventricular rates over a hundred. This can be done even if digitalis has been previously administered in inadequate or unknown dosage. The effects must be carefully observed before repeating a dose.

When no digitalis has been given, 0.5 mg. of ouabain or 0.75 mg. of strophanthin should be the maximal initial dose, with reduced dosage for small individuals. Subsequent doses should be spaced at least thirty minutes apart and none should exceed 0.2 mg. The full dose of 1 mg. of ouabain or 2 mg. of k-strophanthin rarely can be given safely in less than six hours.

In view of the fact that phlebotomy, use of oxygen therapy, and even the employment of cuffs inflated at diastolic pressure on all four limbs usually control pulmonary edema, the use of strophanthin as an emergency drug has become less frequent. To a large extent the pure digitalis preparations given by vein are replacing strophanthins for rapid and certain digitalization. The latter drug is, *par excellence*, a drug for the cardiologist and for residents on large medical services where patients are admitted in a neglected and desperate condition. Strophanthin may be life-saving and irreplaceable by any other agent in such emergency.

Once the state of emergency has passed, it is preferable to use for maintenance a cardio-active drug which is effective orally, as it is not

practical to maintain this effect with the aid of strophanthin. The continued intravenous therapy has several disadvantages. First, there is this sound and general rule in clinical practice to avoid intravenous medication where oral administration can be equally efficacious. Secondly, such practice of repeated injections is unpleasant and more costly to the patient. Thirdly, it creates a greater dependence of the patient on his doctor than is actually warranted. The initial dose of digitalis may be given within twelve hours after the full effect of strophanthin is apparent, but it should be a dose not more than one-fourth the full digitalizing one for that patient.

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CHAPTER VI

Squill

Historical Data

Some of the old time-honored remedies relegated to the medical folklore not infrequently find their way back into modern medicine by virtue of their unfailing qualities. Removed from the dusty shelves of ancient history they reappear in a new garb to shine in the splendor of their rediscovered usefulness. The story of squill serves as another instance of vindication of the old remedies and the popular belief in them by modern scientific research. Squill is one of the oldest drugs known to man. It is also one of the very oldest heart remedies in use today.

Prepared from the bulb of the sea onion (Scilla maritima), it is said to have been introduced into practice by Epimenides or Pythagoras. It is mentioned in the Ebers papyrus, about 1500 B.C., in the prescription appearing below in translation:[1]

Flour of dates	1/4	
Squill	1/32	
Awanw plant	1/3	
Sweet Beer	1/3	dena
Tehebu tree	1/2	

Boil, filter and admininster during four days.

The drug was known to the Egyptians in the time of the Pharaohs as a diuretic in dropsies and was given the symbolical title of ' the eye of typhon.' It was from the Egyptians that Pythagoras (600 B.C.) learned its uses and by introducing acetum scillae added lustre to his name. In the *Syriac Book of Medicine*[2] squill is mentioned as giving relief in asthma, and wine of squill is stated to be good for ' an evil condition of liver and stomach and for those who collect water.' Epimenides, who lived in the thirtieth Olympiad (584 B.C.), employed it

quite extensively. In fact, the drug was held in such high esteem that a temple was erected to it in Pelusium.

Squill has been extolled in the works of the great physicians of the ancient world, like Dioscorides, Celsus, Theophrastus, and others. Galen spoke highly of it.[3] Hippocrates used it externally as a counter-irritant and internally as a purgative and for the relief of cough and dropsy. Later, the external application was abandoned, but the remedy continued to have a reputation as a diuretic, expectorant, and emetic. However, gradually it fell into disuse, possibly because of its tendency to induce nausea and vomiting.

Squill was introduced once more into clinical practice by Van Swieten[4] in the middle of the eighteenth century. He emphasized its clinical usefulness for treatment of dropsy. However, the relation of the diuretic to the cardio-tonic effects escaped recognition for some time to come, although Home,[5] in 1780, noted the slowing of the pulse on administration of the drug. Five years later William Withering published his classic monograph on digitalis and the sea onion was relegated to another period of relative obscurity.

However, in the nineteenth century further observations on squill were recorded sporadically, but the progress made was exceedingly slow. In 1865 the position of squill as a member of the cardio-active group of drugs was recognized by Fagge and Stevenson[6] on the basis of its action on the heart of a frog. These investigators found that this action was similar to that of foxglove. In 1875 Husemann[7] also demonstrated that the active principles contained in squill produced in general the same effect on the heart and general circulation as did digitalis. Some thirty years later Dixon and Haynes[8] prepared a tincture assayed on frogs. Finally, Mendel[9] deserves the credit for arousing renewed interest in the clinical application of the drug. He made extensive pharmacological and clinical studies on the sea onion, and pointed out its usefulness in cases of cardiac insufficiency.

The extremely slow progress made by squill in winning its place in cardio-therapy has been largely due to two factors. First the unreliability of squill as administered in the insufficiently prepared crude galenical preparations must have contributed to its unpopularity. The differences in the varying effectiveness of the preparations of bulbus scillae at times have amounted to as high as 800 per cent, depending upon the variety, the age, and the location of the plant. Secondly, the crude substances with an extremely variable concentration of the active principles also contain a mass of highly irritating resinous com-

pounds. The presence of these irritants makes it almost impossible to administer a therapeutically effective dose without inducing nausea, diarrhea, and irritation of the upper respiratory tract, thus further contributing to the drug's unpopularity.

Only in the course of the last twenty to twenty-five years has modern chemical research made available preparations of squill which can be used safely and effectively in clinical practice. Until quite recently knowledge of the chemical composition of squill was still in a very unsatisfactory state and various authorities have quoted different and frequently hypothetical glycosides as existing in the plant.

Thus Vogel and Tilloy in 1812 were the first to extract from the bulb a substance considered as an active principle. It was given the name scillitin. Thompson extracted scillitit in 1834. In 1860 Mandel distinguished two substances, the poisonous sculein and the non-poisonous scillitin. In 1879 Merck described scillipicrin, scillenin, and scillamarin, which represent purified extracts rather than pure substances. In 1880 Jamersted isolated scillain by means of a precipitation method necessarily involving great loss of glycoside. These substances are all mostly impure mixtures of poorly defined glycosides. To Stoll and Willstratter goes the credit for first isolation of chemically pure cardio-active principles, scillaren A and scillaren B, in 1921. In 1934 methods were developed by Dyas for extraction of the two water insoluble glycosides, scillonin A and scillonin B. With the discovery of these principles squill therapy found its modern use in clinical practice.

Source and Chemical Structure

Squill belongs to the family of lilies (Liliaceae). It is a bulbous plant with white or blue flowers. It grows abundantly in the sandy regions of the Mediterranean littoral, in France, Algeria, Italy, and Asia Minor; a considerable quantity comes from Malta. There are about eighty different varieties known. A variety of squill which grows in Algeria produces red corms. This so-called red squill has served as a source of poison used for the extermination of rats. It contains the same cardio-active principles as the white variety, but in addition there is present a substance which is highly toxic to rats. The chief toxic action of red squill is on the central nervous system.[10] Madaus and Koch[11] maintained that red squill is dangerous to man and therefore should not be used as a source of therapeutic preparations.

In therapeutics the ovoid bulbs are used. The convex part of these consists of scales which represent the base of former leaves. These

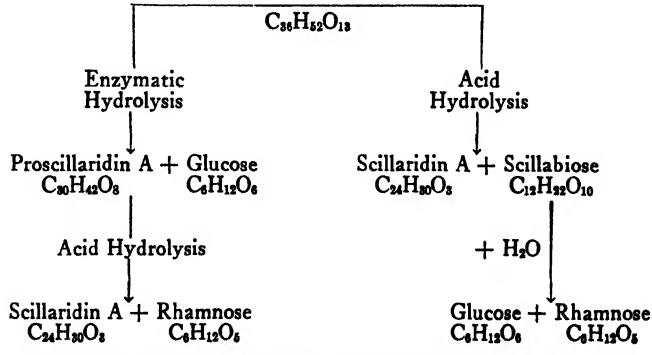
scales reduced to powder have served as a drug in the days of antiquity. In addition to the glycosidal principle, the layers of the bulb contain mucilage, sugar, tannin, traces of iodine, salts, and coloring matter.

Stoll and his co-workers,[12] by making use of special protective methods for the isolation of unstable natural substances, succeeded for the first time in preparing the natural active principles of squill (Scilla maritima) free from inactive accessory substances. Examination of the pure substance confirmed the glycosidal nature, formerly assumed but not proved, of the active principle of the plant. It was found to be composed of at least two substances, showing very marked differences. The less soluble component constituting two-thirds of the mixture, the glycoside named scillaren A, is a crystalline product, whereas the more readily soluble component, scillaren B, is an amorphous compound. Stoll has also demonstrated in the plant the presence of an enzyme which he named scillarenase.

The crystalline scillaren A has been subjected by Stoll to an intensive investigation. On acid hydrolysis it yields the well crystallized aglucone scillaridin A and a hitherto unknown disaccharide scillabiose which can be split by further hydrolysis into rhamnose and glucose. The enzymatic cleavage caused by the enzyme does not attack the linkage of scillaridin with the disaccharide, but yields instead proscillaridin A and glucose. The former, on acid hydrolysis, is split into its two constituent parts, the aglucone scillaridin A and rhamnose.

TABLE IX

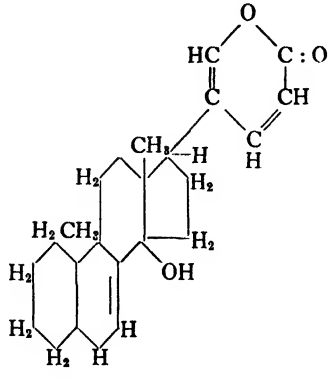
SCILLAREN A



After A. Stoll, *The Cardiac Glycosides*, The Pharmaceutical Press, London. 1937.

The aglucose Scillaridin A possesses one more carbon atom than all the other known aglucones (of digitalis, strophanthin, ouabain),

but otherwise is very similar to them. Its structural formula is reproduced below.



SCILLARIDIN A

Scillaren B, so far, has not been obtained in a crystalline form. Because of its marked solubility it is used for the manufacture of an injectable preparation, while for oral use a product consisting of the mixture of both scillarens, A and B, is employed.

In 1934, methods were developed by Dyas[18] for extracting in pure form the two water-insoluble glycosides, scillonin A and B (now known as urginin A and B respectively). This method was further perfected by Dyas and Ingersoll. The commercially available product marketed under the name of 'Urginin' consists of crystalline and amorphous scillonins combined.

PHARMACOLOGY

Both in animal experiments and in clinical medicine, the glycosides of squill have been found to resemble digitalis bodies in their effects on circulation. These principles embody the full cardiotonic action of squill, exerting as it does an important pharmacodynamic effect on the reserve power of the failing heart.

Effect on the Heart

The drug has been demonstrated to increase cardiac 'tone,' to enhance the force of the systolic contraction and lengthen the diastole of the heart in failure.

Premankur De,[14] in cardiometer experiments made on cats, demonstrated an increase in systolic contraction with slight increase in stroke volume following intravenous injection of scillaren. On perfus-

ing the frog's heart with scillaren in a dilution up to 1:3,200,000, Premankur De produced a cardiac standstill in systole. Stehle, Ross, and Dreyer,[15] using the myocardiograph technique of Cushny, have found an increase in amplitude of the ventricular beat. Working with heart-lung preparations, the authors increased the peripheral resistance gradually to 130 mm. Hg. and the venous inflow to the whole capacity of the venous cannula. As a result the heart weakened, as shown by the dilatation and the appearance of pulmonary edema. The action of scillaren B under these conditions was shown to improve the cardiac output. Concomitantly oxygenation of the blood improved. Peters and Visscher[16] have demonstrated on heart-lung preparations an increase in efficiency of the heart muscle at constant external diastolic volume after administration of scillaren.

The effect on the junctional tissue is similar to that of other cardioactive drugs. Premankur De[14] demonstrated partial A-V block in the frog's heart. Prolonged A-V conduction was found by Chamberlain and Levy[17] in the electrocardiograms of patients after administration of urginin. The same findings have been reported by others. In slowing of ventricular rate in cases of auricular fibrillation this particular action of the drug plays no doubt an important part. Slowing of the heart beating with a regular rhythm has been observed both in the course of animal experimentation[14] and in normal people or patients without heart disease.[17] This slowing in such cases is possibly of vagal or sinus origin. It is not marked in such instances but is quite pronounced in patients in congestive heart failure with regular rhythm and tachycardia, being then concomitant with the general improvement in the state of circulation.

Effect on Venous Pressure, Coronary Circulation, and Peripheral Vessels

With improvement in cardiac efficiency the venous congestion is relieved, the venous pressure falls (if initially elevated), the circulation time decreases, and the vital capacity increases.[17]

Premankur De[14] noted that on perfusion of isolated hearts of rabbits with Locke's solution and scillaren in a dilution of 1:2,500,000, the outflow through the coronaries is reduced during the first few minutes during the initial acceleration of the heart, but is increased again later when the heart is beating more slowly and with increased amplitude.

In experiments on animals Stehle, Ross, and Dreyer[15] found that

the blood pressure almost invariably increased upon administration of the glycoside. Usually the increase was very moderate, but occasionally it was quite marked. At times they found the blood pressure fluctuated considerably. The authors felt that the blood pressure changes were partly of cardiac origin and partly due to the peripheral effect (vaso-constriction).

Dubinski[18] is of the opinion that the rise of blood pressure in the first few minutes is purely of 'hemodynamic' origin, the peripheral effect occurring later. Premankur De also found a slight rise in blood pressure. Rothlin[19] states that 'blood pressure is always distinctly raised by the glycosides of squill.' His impression was that at least in experiments on animals this property is more marked for the glycosides of squill than for those of digitalis. Clinically there is no specific effect on systolic or diastolic levels of blood pressure,[17] as in the case of digitalis.

Fahrenkamp and Nocke[20] using frogs have reported vaso-constriction on administration of scillaren. Employing only small doses, these investigators observed vaso-dilatation. Vaso-constriction has also been found by Stehle, Ross, and Dreyer.[15] Premankur De[14] has investigated the action of the glycoside on blood vessels in animals by oncometer and perfusion experiments. The blood vessels of the frog were perfused with saline through the innominate artery and when the rate of flow from the veins was constant a saline solution, containing 1:5,000 to 1:10,000 of the active principle, was substituted. This caused at first a slight increase in the outflow, which was followed by a gradual and pronounced diminution. The same results were obtained by using Dixon's apparatus for perfusing isolated limbs of a rabbit. Rothlin,[19] on observing the behavior of the blood vessels of the kidney, of the intestine, and of the extremities *in vivo,* noted that with very small 'therapeutic' doses of 0.05 mg. of the glycoside there was dilatation of the vessels of the extremities and kidneys, but at the same time constriction of the vessels in the intestine. *In vitro,* solely a distinct constriction of the blood vessels was observed in the kidney, the intestine, and the ear of a rabbit and the extremity of a frog when 'borderline' doses were used (0.5 cc. of a solution of 1:500,000 to 1:1,000,000). He believed that these doses gave rise to a concentration which is not far off the concentrations reached therapeutically, and arrived at the conclusion that the therapeutic effect of scillaren is partly based on its action on the blood vessels.

Diuretic Effect

A diuretic effect of squill glycosides has been noted in experimental animals.[14] Rothlin[19] states that he has been able to demonstrate a diuretic action in normal animals. He felt that this could not be the result of a rise of blood pressure, ' as the administration of other glycosides [not derived from squill] did cause an increase of blood pressure, but not of diuresis.' Some investigators have expressed a belief that the squill glycosides exert a direct action on the renal epithelium and thus bring about an increase in urinary output. Perrin,[21] on the assumption that such effect does exist, recommends the use of the glycoside in cases of renal insufficiency in conjunction with xanthine diuretics. Bonnarme[22] is of the opinion that in treatment of renal azotemia the action of the glycoside is superior to that of xanthine diuretics. Florentin,[23] on the basis of physiological and pathological studies, reached the conclusion that the site of action is on the convoluted tubules but leaves open the question of the possible mechanism responsible for this effect. Nervous and humoral mechanisms have been suggested by others (Carnot, Blum). Stroé and Klinger[24] have used scillaren in cases of post-scarlatinal nephritis with azotemia, edema, or both, claiming good results. In no case did the appearance or increase of formed elements in the urine give evidence of renal damage by the drug. Trant has used it as a diuretic in cases of portal cirrhosis.

In cases of congestive heart failure squill has been repeatedly demonstrated to act as an effective diuretic. In all likelihood such diuretic effect is not secondary to any direct stimulating action on the kidneys, but rather, as in the case of digitalis, probably is due to improvement in the state of circulation.

Effect on the Electrocardiogram

The changes in the electrocardiogram produced by the glycosides of squill resemble those caused by digitalis. Maher and Sittler[25] have investigated the effects of urginin on twenty-five cardiac patients, studying especially the effect of therapeutic and toxic doses on the electrocardiogram. They found these effects on the electrocardiogram to be characteristic and fairly consistent, particularly with regard to RS-T segments. The changes in the RS-T segments were similar to those seen with digitalis as described originally by Cohn and Pardee. In those patients who were studied with both urginin and digitalis the changes were similar with equivalent amounts of each drug over equal

periods of time. In therapeutic doses the effects of urginin, like those of digitalis, appeared to be limited to changes in contour of RS-T segments, slight prolongation of the P-R interval and occasional premature contractions. Frequent premature beats, marked prolongation of the P-R interval and the production of auricular fibrillation were noted as the effects of over-dosage in patients intolerant to the medication. Similar findings have been reported by other investigators.[26] Windle[27] recorded a complete heart block in a patient as a result of squill. Partial inversion of the T-waves has been observed by White, Balboni, and Viko,[28] and others.[17]

Toxic Effects

The toxic effects of squill glycosides are similar to those of digitalis. Carr and Mayer[29] state that in their experience cardiac irregularities are likely to be the first signs of dangerous intoxication. Nausea may precede the appearance of arrhythmias. They believe that nausea of intoxication with squill glycosides (urginin) signifies a more advanced grade of intoxication than in the case of digitalis. They warn that nausea and cardiac irregularities occurring in the course of treatment with urginin are symptoms which call for the immediate discontinuance of the drug. They mention bigeminal rhythm and auricular fibrillation among the arrhythmias caused by urginin. Maher and Sittler[25] have noted auricular, nodal, and ventricular premature contractions of ventricular origin. In a few patients auricular fibrillation developed; this reverted to sinus mechanism on discontinuance of medication. Nodal rhythm has been noted.[30] Vomiting, diarrhea, dizziness, and flushing have also been reported.[17,30] Heart block,[14] premature contractions, and ventricular fibrillation[15] have been produced by scillaren in experimental animals. Production of partial A-V block by the glycoside in human subjects has already been mentioned. Changes in the electrocardiogram have been observed to last for as long as seventeen days after the drug was discontinued.

The toxicity of different glycosides of squill varies when tests are done on experimental animals. Thus Rothlin[19] has found that the two components of scillaren (A and B) possess different but corresponding toxicities for cold blooded and warm blooded animals. Scillaren A contains 1,000 frog doses per mg. While 1 mg. of scillaren B is lethal for 7 kg. of cat, 1 mg. of scillaren A is lethal for 4.4 kg. of cat.

Riseman and London[31] have recently described some of the properties of a substance which is obtained by condensing a disodium salt of a mix-

ture of aglucones isolated from squill (presumably scillaridin A and B) with two molecules of theophylline. They have demonstrated by electrocardiographic studies that the substance so obtained (theophyllinated scillaridin) differs in its action from either a mechanical mixture of theophylline with the aglucones, or from the original glycosides. This is the first report of an attempt to modify the action of a cardiac glycoside by chemical combination with a xanthine derivative. DeGraff and Lehman[82] have indicated in the report of their investigations on theophyllinated scillaridin in the cat that this substance appears to be appreciably less toxic than either the aglucone alone or the glycosides, although the toxic effects qualitatively are essentially similar. Lorber, Greenberg, and Visscher[83] have studied the efficiency-increasing and toxic effects of the substance on isolated cat hearts and reached the conclusion that it exhibits marked cardiotonic properties and low toxicity. Dimethylxanthine genate has not yet been studied extensively in clinical practice.

Absorption, Fixation, and Cumulation

Squill glycosides have been demonstrated to be well tolerated, well absorbed, and rapidly active both in animals and man. On post-mortem examination of animals to which toxic doses were administered no signs of irritation have been noted in the gastro-intestinal tract either grossly or microscopically.[14]

Straub and also Rothlin[19] have found that the glycosides of squill can be more readily washed out of the intoxicated isolated heart of a frog than the glycosides of digitalis. They concluded that squill glycosides are not fixed by the heart as strongly and are thus less cumulative than digitalis. Climenko[84] found that the reversibility of the action of a series of cardio-active glycosides on the isolated turtle heart may be expressed in the following way: Urginin is more readily reversible than ouabain, which is more readily reversible than digoxin, which is more readily reversible than digitoxin. The author states that the cumulative effect of urginin is half as great as that of ouabain and one-fifth as great as that of digitoxin. Wallace and Van Dyke[85] give the same comparative figures for cumulative effects of urginin and ouabain, although the acute toxic effects produced by continuous intravenous injections were the same. On the other hand, they are of the opinion that scillaren is more cumulative than ouabain, this being contrary to the view of Straub. Eismayer[86] remarks that cumulation of scillaren is but slight when given orally, but on intravenous injection it is more cumulative, however, than strophanthin. He warns that patients treated by scillaren intravenously must be carefully watched. Although Chen, Ling

Chen, and Anderson,[87] in studying the potency of several cardiac principles by Hatcher-Brody and U.S.P. Frog methods, found scillaren near the bottom of the list in the order of persistence of action from high to low, cumulation appears to be of sufficient magnitude to allow useful application in clinical practice. With regard to urginin, Carr and Mayer[29] comment that one notable feature of the drug is the long duration of its action; marked slowing of the ventricular rate or bigeminal pulse appeared in a number of instances several days after the medication had been stopped.

Koerner[88] states that scillaren when injected intravenously resembles strophanthin in rapidity of action but that in cumulative properties it stands closer to digitalis. According to Weese,[89] scillaren is less cumulative than digitoxin and is eliminated more quickly. Zwillinger[40] is also of the opinion that the glycoside is quickly eliminated.

Standardization and Preparations

Considerable work has been done with different methods of bio-assay of squill products.[41,42] These, however, will not be discussed here, as with the isolation of pure active principles, which can be standardized gravimetrically, bio-assay ceases to be so essential. The old official preparations of squill, such as tinctures, should be relegated to antiquity, as there is no reason for using them now that purified drugs are available. It may be mentioned in passing that biological assay by the intravenous cat method has shown that 1 mg. of urginin has an average potency of 4.26 cat units; thus one cat unit contains approximately 0.20 mg. of the drug.[48] In the case of scillaren A and B, one cat unit represents 0.18 mg. and 0.14 mg. of the active principle respectively.

Of the official preparations of squill there are a number. These are: Syrupus scillae compositus (from fluid extract); Mistura pectoralis (from fluid extract), N.F.; Acetum scillae; Syrupus scillae (from vinegar); Tinctura scillae, N.F., Br.; and Fluidextractum scillae, N.F., Br. U.S.P. X required that squill be assayed by a method essentially similar to that of digitalis, but neither the Br. nor N.F. mentions any assay processes. All these preparations are obsolete and should not be used.

N.N.R., 1942, recognized scillaren B and also under the name ' Scillaren ' a mixture of crystalline scillaren A and amorphous scillaren B in the proportions in which they occur in the fresh drug. This mixture is more soluble in aqueous solvents than is scillaren A alone and remains stable over a long period of time. Scillaren B, because of its marked solubility, is used in preparations for parenteral administra-

tion. N.N.R. also recognize a mixture of the two non-water soluble squill glycosides (crystalline scillonin A and amorphous scillonin B) under the name 'Urginin.'

Urginin is available in 1 mg. tablets (formerly also in 0.5 mg. tablets). Scillaren is available for oral use in tablet form containing .8 mg. of the glycoside, in liquid form, 20 drops containing about .8 mg. of the active principles and in suppositories containing 0.5 mg. of the drug. For parenteral use scillaren B is dispensed in 1 cc. ampules containing 0.5 mg. of the glycoside. All these preparations have been found to possess uniform biological potency and a high degree of stability.

Clinical Applications

The indications for therapy with squill glycosides are comparable to those of digitalis. The drug has been quite popular in European clinics where scillaren is the squill preparation of choice.

Kapff[44] considers scillaren preferable to and safer than digitalis in patients with partial heart block because of the comparatively rapid elimination of the glycoside. Fahrenkamp feels that scillaren is less apt to produce signs of intoxication than digitalis or strophanthin. Berger[45] thinks that squill derivatives give results comparable to digitalis. He successfully treated with scillaren over one hundred patients in congestive failure with degenerative and valvular types of heart disease. Subjective symptoms were relieved, diuresis was promoted, and edema with heptaic congestion disappeared. In cases where intravenous therapy may be advisable, as in severely decompensated patients, he advocates the use of an initial dose of 0.3 cc. of scillaren B daily for the first two days, then increasing the dose every second day, first to 0.5 cc. then to 0.8 cc. and 1 cc. Intravenous therapy is followed by the oral adminstration of two tablets three times daily for the first two or three weeks, later reducing this amount to the maintenance dose of two or three tablets daily. In the less severe cases of cardiac insufficiency oral therapy alone suffices; two tablets four times daily for one week, subsequently reduced to the suitable maintenance dose.

Eismayer[46] recommends the following dosage: One-half of a tablet of scillaren three times daily, increasing gradually to five tablets daily; for intravenous injection 1 cc. a day at intervals of two to three days, depending on the patient's condition.

Bach and Berr[47] regard scillaren as a valuable remedy in the therapy of heart disease. They feel that the comparatively simple dosage and the fact that it is well tolerated allow broad clinical application of this

glycoside. These authors have employed one-half of a tablet, 0.4 mg., from eight to ten times daily for the first four to six days, followed by one one-half tablet four times daily. The latter dose is varied according to the condition of the patient. To obtain rapid effect they have administered scillaren B intravenously. At first 0.4 cc. (0.2 mg.) is given cautiously; this is increased to 1 cc. (0.5 mg.) if it is well tolerated. The authors report an excellent digitalis-like effect on the heart in failure.

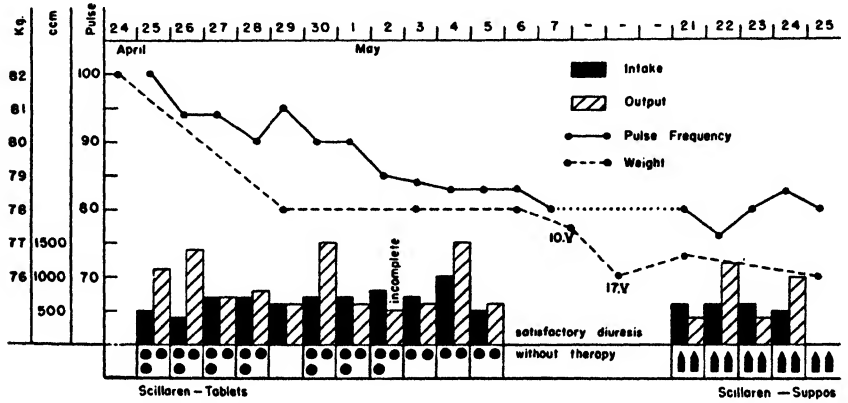


FIG. 19. Patient in congestive failure. Effect of scillaren (tablets and suppositories) on pulse rate, weight and urinary output. (From F. Bach and A. Bezz, *Deutsche Medizinische Wochenschrift*, no. 40, 1935.)

Solis-Cohen and Githens[48] state that 'In dropsy dependent upon heart failure or congestion of the kidneys and sometimes in ascites or cirrhosis of the liver, squill acts as an effective diuretic, causing a rapid draining of the fluid from the tissues or cavities of the body.' In this country squill and its derivatives are not used as diuretics in cases of edema of non-cardiac origin, such as nephritis or portal cirrhosis.

Perrin[49] states: 'Without criticizing digitalis which is and will remain a cardio-active drug of choice, we are in the position to affirm that in each case of myocardial insufficiency . . . scillaren, administered in proper doses, gives excellent results.'

Carr and Mayer[29] have reported favorable clinical experience with scillonin (urginin). Their series of eighty-five patients included cases of degenerative and valvular (rheumatic and syphilitic) heart disease. Satisfactory therapeutic effects were obtained. A dose of from 8.0 to 12.0 mg. depending on the weight of the patient may be given within four days to patients who have not taken a drug of the digitalis group within two weeks. The maintenance dose was found to be approxi-

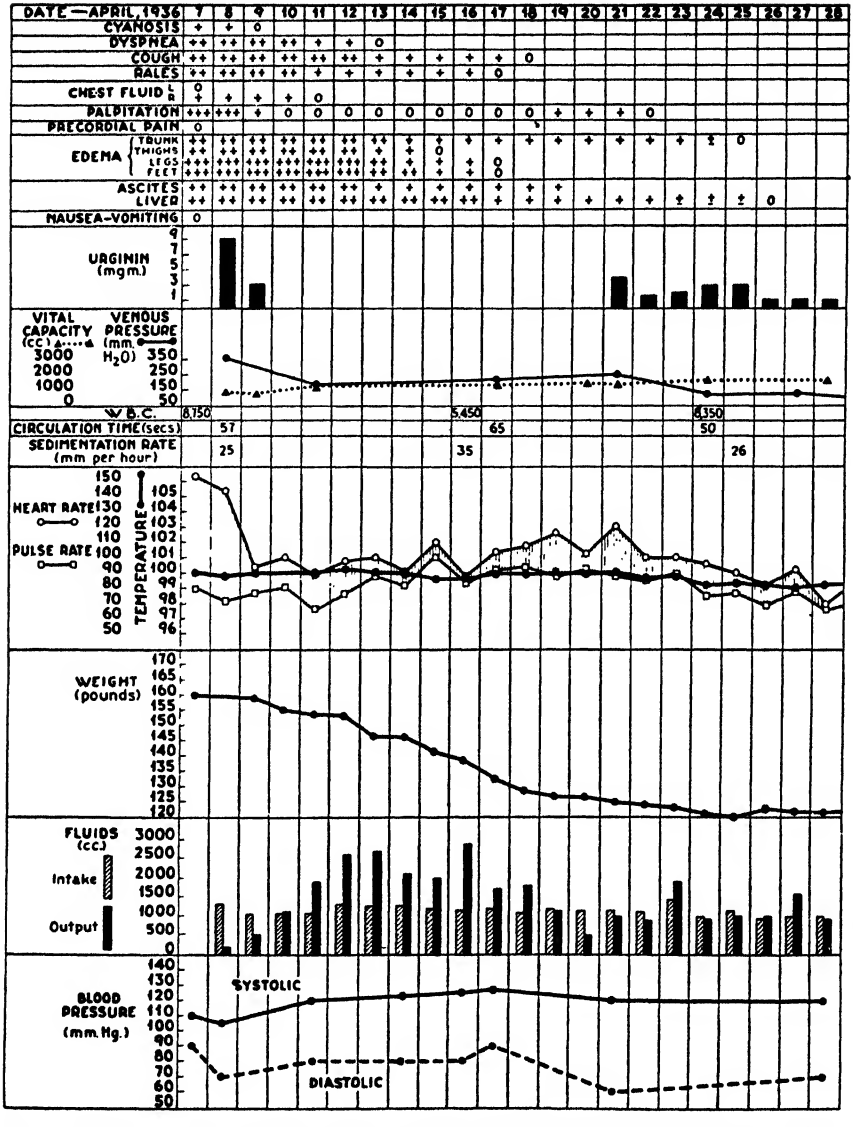


FIG. 20. Patient with advanced cardiac insufficiency. Administration of 12.0 mg. of urginin in two days was followed by partial relief of symptoms, fall in venous pressure by means of congesting cuffs on the thighs produces a small but significant inmarked diuresis. There was no significant change in arterial blood pressure. There were no toxic effects. After stopping urginin therapy, the heart rate became progressively more rapid beginning on the sixth day. The venous pressure rose and the urinary output diminished. Additional doses of the drug, smaller than those originally given, produced greater relief of symptoms and signs of cardiac insufficiency, with further fall in venous pressure and renewed diuresis. (From F. L. Chamberlain and R. L. Levy, *Am. Heart J.*, vol. 14, 1937.)

mately 0.5 mg. per day, but might be as low as 0.33 mg. The authors point out that the drug should not be used as a substitute for digitalis in the presence of frank digitalis intoxication. They conclude that urginin is of advantage in certain persons who take digitalis with difficulty because of gastric distress early in the course of medication.

Maher and Sittler[25] administered urginin to twenty-five patients with heart failure. The dosage ranged from 1.0 to 3.0 mg. daily for varying periods. There was a wide variation in the degree of effect produced, implying either difference in absorption or in the response of the patient to medication. The ventricular rate was decreased in twenty-one of the twenty-five patients. The cardiac slowing occurred in the presence of sinus rhythm as well as in auricular fibrillation. The four exceptions included one patient with bronchopneumonia which caused his death, two patients with uremia from which they succumbed, and one patient with chronic auricular flutter. Boden and Neukirch[50] reported a patient with auricular flutter who regained a sinus mechanism under the influence of squill and relapsed into auricular flutter when the squill was discontinued.

Chamberlain and Levy[17] studied the effects of urginin on sixty-two patients. The patients were hospitalized and carefully controlled before and during administration of the drug. In patients with cardiac insufficiency urginin administered orally exerted an action like that of digitalis. The signs and symptoms of congestive failure tended to disappear. These effects were noted in the presence of regular rhythm as well as auricular fibrillation. In all cases of auricular fibrillation there resulted ventricular slowing, while in those with regular rhythm the slowing of cardiac rate occurred in about one half of the cases. The authors found the therapeutic potency of urginin, in terms of cat units, to be about one-half that of digitalis. This difference might be attributed to less complete absorption or more rapid elimination in the case of urginin. When no digitalis or urginin had been given for at least ten days preceding, a satisfactory scheme of dosage was found to be as follows: 1.5 mg. three times a day for two days, followed by 1 mg. twice daily until the desired therapeutic effect is obtained. The daily maintenance dose ranged from 0.5 to 2 mg. with the average of 0.92 mg. The total effective dose (the full amount given less 1 mg. theoretically excreted each day) ranged from 6.5 to 14 mg., with the average of 9 mg. The duration of effect was variable. In cases of auricular fibrillation, the effect on ventricular rate began to diminish in from three to ten days. One patient, nauseated by digitalis, took urginin without dis-

tress. Another had diarrhea after taking digitalis, but none following urginin therapy.

Vander Veer, Stroud, and Edwards[80] studied the clinical effect of urginin on forty-two patients. In this series there was one group with congestive failure who had previously received no preparations of digitalis and were treated in the hospital. The other group consisted of out-patients with chronic auricular fibrillation who had been previously controlled on one or more preparations of digitalis. In the first group the drug was given in divided doses over a period of several days and clinical improvement was usually evident by the fifth or sixth day. The amount of the drug necessary for full therapeutic effect over that period varied from 12.5 to 29.5 mg., with the average of 18 mg. Of eighteen patients in the other group (with auricular fibrillation and previously maintained on digitalis), eleven were equally well controlled on urginin therapy. In two patients the ventricular rate was well controlled, but the patients did not seem as well as when they were taking digitalis, although frank cardiac decompensation did not occur. Difficulty in controlling the ventricular rate was encountered in one case after apparently sufficient dosage. In two patients congestive heart failure developed during the course of urginin therapy, despite the fact that the doses were increased to the point of toxicity; they improved with administration of digitalis. The authors concluded that urginin possesses actions similar to digitalis. They state that the ability to slow the ventricular rate in patients with auricular fibrillation 'was fully as striking as that of digitalis.' The rapidity of action when given orally was comparable to digitalis in the equivalent dosage. In a few patients who had difficulty in taking digitalis because of subjective distress, urginin was effective without producing these symptoms.

Levy[51] suggests that squill glycosides be substituted for digitalis in treatment of cardiac arrhythmias (premature contractions) when digitalis is poorly tolerated. In his book on *Heart Disease*, White[52] states: 'The active principle of squill may be used by mouth advantageously in the very few cases who need digitalis but cannot take it because of a hypersensitive reaction or very strong prejudice against the taste.'

Summary and Conclusions

The glycosides of squill are effective cardiac remedies. Their action on the heart muscle and the conducting system is similar to that of digitalis and other cardio-active principles. However, they do not appear to offer any advantage over digitalis. Their clinical application

may be reserved for those patients in whom digitalis induces nausea, vomiting or diarrhea, or who, for some reason or other, have a prejudice against the latter drug. Intolerance to digitalis is encountered but very rarely.

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CHAPTER VII

Other Cardiotonic Agents of Plant Origin

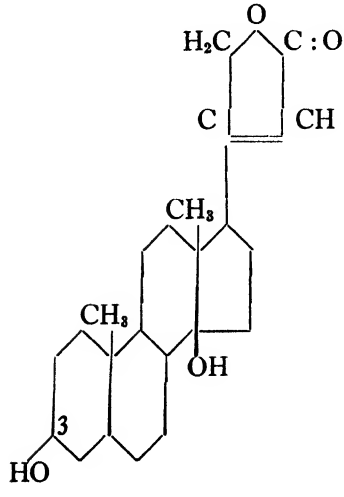
Thevetin

The plant Thevetia neriifolia is indigenous to South America and the West Indies. It is cultivated in the East Indies, India, West Africa, and the Hawaiian Islands, where it is used chiefly for ornamental purposes. The plant belongs to the family Apocynaceae, which also includes different species of Strophanthus. The tree bears fruits of yellow oleander, termed the ' be-still nut ' in the Hawaiian Islands. The fruit yields dark-brown, hard-shelled nuts with kernels which have been known to be poisonous as early as the sixteenth century.

In 1863, DeVry[1] isolated from the nuts of Thevetia neriifolia a glycoside to which he gave the name of thevetin. Its chemical composition has not yet been definitely established. Its empirical formula is thought to be $C_{29}H_{46}O_{13}.2H_2O$. It is believed to consist of an aglucone named thevetigenin in combination with two molecules of glucose and possibly one molecule of digitalose, the same sugar found in the glycoside digitalin obtained from the seeds (not the leaves) of Digitalis purpurea. This substance is soluble in alcohol and to some degree in water and has the melting point of about 193° C.

König and Husemann[2] were the first to demonstrate with thevetin a digitalis-like action on the heart. They also reported on necropsy of animals congestion of the stomach and liver. Descourlitz, quoted by these authors, observed nausea as well as shivering and nervous manifestations in a Negro who had eaten a kernel of the Thevetia plant. Another early report on poisoning in man by the be-still nut was made by Balfour and Maclagen,[3] who described the occurrence of nausea and a peculiar form of vomiting not accompanied by any distress or

THEVETIGENIN



retching, but in association with marked diarrhea in two boys who had eaten the seeds of Thevetia neriifolia. Arnold[4] reported a fatal case of poisoning in a child who developed nausea, vomiting, and diarrhea and apparently died as a result of toxic effects of the poison on the heart. On injecting thevetin intravenously in cats, Chopra and Mukerjee[5] noted the stimulation of intestinal movements, which they attributed in part to peripheral vagal stimulation and in part to direct action on smooth muscle, as the effect lessened to a great extent upon the administration of atropine. They also reported a stimulating action on the heart when the drug was administered in small amounts. Larger doses had a depressing effect eventually leading to cardiac standstill.

Chen and Chen became interested in the plant when they received a sample of the nuts forwarded to them from the Hawaiian Islands by Arnold, who witnessed the fatal case of poisoning above mentioned. These investigators[6] isolated from the nuts thevetin and subsidiary glycosides in pure form. They also carried out valuable pharmacological studies on this principle.[7,8]

The chief mode of action of thevetin is its effect on the heart. In experiments on frogs, the injection of the glycoside into the lymph sac or perfusion into the inferior vena cava resulted in systolic ventricular standstill. In experiments with the mammalian heart it has been demonstrated that while small doses have a stimulating effect, the

larger doses depress and stop the ventricles.[5] During stimulation, the cardiac output is increased. Also the coronary outflow is said to increase, but it diminishes during the intoxication stage induced by larger amounts of the active principle. Typical changes of digitalis-like action have been shown in the electrocardiographic tracings on cats, consisting of inversion of T-wave, bradycardia, prolongation of P-R interval, auriculoventricular dissociation, ventricular tachycardia, and ultimately ventricular fibrillation.[7]

Thevetin when administered in large doses to experimental animals caused a sustained rise in blood pressure.[9] It induces nausea and vomiting in pigeons, cats, or dogs. In addition to stimulating intact and isolated intestines, in appropriate concentrations the drug also stimulates the uterus and the urinary bladder, the action being probably on the smooth muscle.[5,7]

In experiments on cats, thevetin has been shown to have a persistence of action comparable to ouabain.[9] Forty-seven per cent of the fatal dose may remain in circulation for more than five hours, and 71 per cent for more than twenty-two hours. Up to 82 per cent may be completely eliminated in twenty-four hours. Haag and Pennington[10] have found the persistence of effect of thevetin to be less durable than in the case of ouabain. They concluded that the former drug ' is one of the most rapidly eliminated (physiologically) digitaloids yet described.' Thevetin has been demonstrated to be easily absorbed in animals, both when administered *per os* or by subcutaneous injection.

In terms of the fatal dose, smaller quantities of thevetin are required to produce the first appearance of prolongation of P-R interval and maximal slowing of the heart than in the case of digitoxin or ouabain. On the basis of the minimal emetic dose as determined in cats, thevetin is one-fifth as emetic when compared with ouabain, gram for gram.[7] At the same time, the former drug is one-seventh as toxic as far as other manifestations are concerned, but it is also only one-seventh as active as ouabain. The exact potency of the crystalline product has been determined by Chen and Chen.[7] The frog minimal systolic dose was found to be between 0.004 and 0.005 mg. per gm. and the cat unit 0.85 mg. per kg., as compared with the frog minimal systolic dose of 0.0005 to 0.0006 mg. per gm. and the cat unit of 0.12 mg. per kg. for ouabain.

Arnold, Middleton, and Chen[9] have studied the action of the glycoside on normal human subjects and cardiac patients. Contrary to the experience of Husemann,[2] who believed that it caused abscess for-

mation upon injection, these investigators failed to observe necrosis, either in animals or in men, on intradermal, subcutaneous, or intramuscular administration under aseptic precautions. However, they found intramuscular injection too irritating in man, while no ill effects such as evidence of local irritation or thrombosis were apparent on injection into a vein. Upon oral administration of thevetin to normal individuals in doses of from one to five cat units, there regularly occurred a fall in the pulse rate ranging from nine to twenty beats per minute. The degree of cardiac slowing bore no direct relation to the dose. The maximal effect became apparent in two to three hours. The blood pressure changes were equivocal. The incidence of rise and fall in systolic blood pressure was about equal. The authors also administered the drug to patients in congestive heart failure. Regardless of the route of administration, the cat unit equivalent served as the standard of dosage. The individual dose of thevetin never exceeded five cat units, nor the daily total ten cat units. Cardiac slowing was observed in cases of both auricular fibrillation and regular rhythm. There was a concomitant fall in venous pressure in the majority of patients in whom this determination was carried out. The changes in blood pressure were not decisive. There was a rise in systolic pressure in some patients and a fall in others. The control of decompensation was marked in a number of patients and diuresis resulted in the presence of pronounced edema. In a few patients it was noted that thevetin was capable of maintaining full therapeutic effect when utilized in place of digitalis at maintenance levels. The effect on the electrocardiogram closely paralleled the results of digitalis therapy. Lengthening the P-R interval, inversion of the T-wave and deviation of the S-T segments were all observed. Premature contractions and disturbances of conduction occurred as toxic manifestations. Patients receiving thevetin intravenously were remarkably free from gastro-intestinal symptoms of intoxication; anorexia, abdominal discomfort, or cramps, and diarrhea occurred in only very few cases. On the other hand, oral administration of galenical preparations of thevetia caused a notable incidence of gastro-intestinal disturbances. These galenical preparations of defatted kernels, such as the tincture and the powder, prepared by the authors, may possess additional ingredients which are irritating to the digestive tract and therefore appear to be clinically unsuitable, the experience with them being very similar to that already mentioned in the case of crude preparations of squill.

Middleton and Chen[11] have made a systematic study of the action

of thevetin administered orally to patients in cardiac decompensation. In the majority of patients the favorable results obtained were comparable in all details to those produced by digitalis. Thus, the cardiac slowing, relief of dyspnea, decrease in venous pressure, increase in vital capacity, diuresis with loss of edema, and typical electrocardiographic changes uniformly occurred. There were also a number of therapeutic failures. While 60 per cent of the patients were practically free from untoward symptoms, in the remaining 40 per cent there developed varying degrees of gastro-intestinal reactions. Among these, cramps and diarrhea were more frequent than anorexia, nausea, and vomiting. In a few instances the adverse effects preceded any evidence of circulatory improvement, but in other instances they appeared either simultaneously or some time after clinical improvement had become apparent. With thevetin the occurrence of cramps and diarrhea is more conspicuous than anorexia, nausea, and vomiting as compared with digitalis. It is possible that doses smaller than those employed by the authors would be adequate for attaining the desired therapeutic result without at the same time producing marked gastro-intestinal symptoms.

Noble and Chen[12] have found thevetin useful in reducing tachycardia of hyperthroidism. In the presence of cardiac failure accompanying thyrotoxicosis, the drug was considered by the authors as an important pre-operative measure. A case showing the successful use of thevetin in post-operative thyroid crisis has been reported.[18] Further investigations are still in progress.

Recent clinical studies on thevetin have been carried out by Gold and his associates.[13a] They have investigated the speed of action of the drug and its absorption from the gastro-intestinal tract in eight patients with auricular fibrillation and heart failure. In several instances the effects of the oral and intravenous doses were compared in the same patient. Thevetin was found to be slowly and irregularly absorbed from the gastro-intestinal tract, being less effectively absorbed than digitalis leaf. Large oral doses of thevetin frequently caused diarrhea by local action and occasionally vomiting. These findings stand in constrast with digitalis, after which vomiting from the local action of large oral doses is frequent and diarrhea comparatively rare. The authors found that the intravenous injection of thevetin produced digitalis-like effects upon the heart more rapidly than any glycoside of the digitalis series known at the present time. The full effect was noted to develop in a period of about six minutes after the beginning

of the injection. However, the duration of action was very brief, the effects of a fully digitalizing intravenous dose disappearing almost completely in a period of from two to three hours. Again, this is more rapid than for any other cardiac glycoside. The authors have concluded that: 'The combination of properties, extremely rapid in development and rapid in elimination, suggests interesting possibilities for the use of thevetin by intravenous injection for the treatment of acute heart failure with pulmonary edema, critical conditions in which effective digitalization in a matter of minutes rather than hours may prove decisive. Since, in such cases, the danger of overdigitalization is relatively great, the rapid excretion of thevetin provides an important factor of safety.' More clinical studies on this drug are needed before its widespread clinical application becomes warranted.

Various Glycosides of Plant Origin

There are various other glycosides of plant origin besides those already mentioned in this book. The other poisonous plants yielding cardiac glycosides are Convallaria majalis, Antiaris toxicaria, Helleborus niger, Adonic vernalis, Nerium oleander, and Periploca graeca.

A very active crystalline glycoside, convallatoxin, has been isolated by Karrer from Convallaria majalis, a Liliaceae. The plant (Lily of the valley) was used for many years in Russia for treatment of dropsy. The glycoside gives the nitroprusside reaction and possibly belongs to the strophanthin and digitalis group of unsaturated lactones.

Antiaris toxicaria is a tree of the Malayan Archipelago and yields a sap from which two cardiac glycosides have been obtained by Kiliani. They are called α- and β-antiarin with a tentative empiric formula of $C_{27}H_{40}O_{10}$. While the aglucone antiarigenin is the same in both glycosides, the sugars are different. β-antiarin yields rhamnose on hydrolysis, while the sugar of α-antiarin is antiarose, an isomer of rhamnose.

Nerium oleander belongs to the family Apocynaceae. The poisonous properties of this plant were known in antiquity. A crystalline product, oleandrin has been prepared from the leaves. Windaus and Westphal have shown it to be a glycoside with an empiric formula of $C_{31}H_{48}O_9$. On hydrolysis it yields digitaligenin and a sugar which is probably digitalose ($C_7H_{15}O_6$), a methyl-ether or a methyl-pentose.

Schindel and Braun[14] have made studies on the glycoside foliandrin isolated from the Palestinean oleander bush (Nerium oleander). The authors felt that this glycoside was different in several respects from

the principles so far isolated from various oleander species. It was shown by means of continuous electrocardiographic tracings from a cat's heart, that upon intravenous administration its action was identical with that of the principles belonging to the group of strophanthin glycosides. The authors felt that the drug should therefore be considered a ' strophanthinoid.' However, in contradistinction to strophanthin, it displayed its full cardiac effect upon peroral administration.

From Periploca graeca, belonging to the family Asclepiadaceae, a crystalline glycoside, periplocin, has been isolated by Lehman. The aglucone peroplogenin is obtained on hydrolysis. Jacobs and Hoffman have shown Lehman's glycoside to be only one of a mixture which occurs in the plant. By treating the extract of the same plant with the enzyme, strophanthobiase, these investigators were able to crystallize periplocymarin. Lately Stoll and Rentz isolated periplocin also giving rise to periplocymarin on enzymatic hydrolysis.

From the seeds of Digitalis purpurea a glycoside has been isolated described under the name ' Digitalinum verum.' From this substance Kiliani obtained on hydrolysis the aglucone digitaligenin and two sugars, digitalose and glucose. More recently Windaus and collaborators have determined the empiric formula of this glycoside to be $C_{36}H_{56}O_{14}$, while the empiric formula of the aglucone was found to be $C_{23}H_{30}O_3$. These workers have also shown that digitaligenin does not occur pre-formed in the glycoside moiety, but is instead a dehydration product of the original aglucone, which is probably gitoxigenin. Thus a close relationship has been demonstrated between Digitalinum verum and the glycoside oleandrin, which is obtained from a different species of plant. This digitalin (Digitalinum verum) should not be confused with digitaline Nativelle or the German and French digitalin. German digitalin is a mixture of glycosides obtained from digitalis seeds, while the French product represents a mixture of glycosides from digitalis leaf.

The cardio-active principles of animal origin will be discussed in the following chapter.

Summary and Conclusions

Thevetin may show promise of being an effective cardiac drug However, further clinical investigations are necessary for ascertaining its clinical usefulness.

The other glycosides mentioned in this chapter are chiefly of academic interest.

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CHAPTER VIII

Cardiotonic Glycosides of Animal Origin and a Cardiotonic Alkaloid

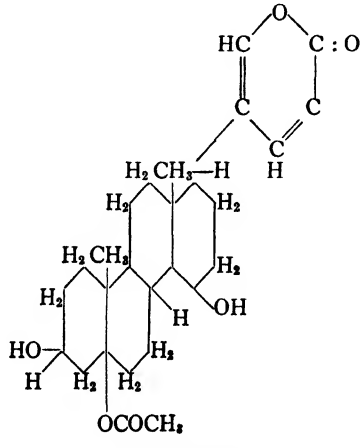
Toad Poisons

The secretions of the skin glands of toads are known to contain poisonous nitrogenous substances with sterol-like constituents. These so-called toad venoms exert physiological activities similar to those of the cardiac glycosides. Their definite medicinal qualities have been recognized for centuries. The Chinese have long employed the dried preparation from a common toad as a drug. In China the remedy is known as Ch'an su and in Japan as Senso.[1] Before the introduction of foxglove by William Withering in 1785, dried and powdered toad skins were in common use for treatment of dropsy.

The material secreted by the skin glands can be obtained from dried toad skins or from the living animal. The ' parotid ' glands located behind the eyes are particularly abundant in this substance. The role of the venom in the animal organism is not known; it is not believed to be used either in self-defense or in the performance of any body function.[2] Abel and Macht[3] were the first to isolate an active principle in pure form from the secretion of the tropical toad, Bufo agua; the substance was named bufagin.

Extensive chemical studies of the toad poisons have been conducted by Wieland and collaborators. Chen and Jensen have also made valuable contributions. It has been shown that the active poisons occur in the form of conjugated compounds analogous to cardiac glycosides, for on hydrolysis of a conjugated compound, or bufotoxin, an aglucone (bufagin) is liberated. The terms 'bufagins' and 'bufotoxins' are employed generically. For each specific principle is prefixed the name of

the species of the toad or some reference to the place where the toad is found. There are a great number of these substances known, obtained from different species of the animal. The best known example is the compound bufotoxin, obtained from Bufo vulgaris by Wieland and Allen.[4] Its empiric formula is $C_{40}H_{62}O_{11}N_4$ and it represents the suberylarginine ester of the aglucone bufotalin. The structural formula of bufotalin appears below:



BUFOTALIN

Thus it can be seen that bufotalin has a chemical structure very similar to that of aglucones of plant origin. It appears that scillaren A has a closer resemblance to bufotoxins and bufagins than digitoxin, strophanthin, or thevetin.[5]

All the respective bufagins and bufotoxins have approximately the same solubility. By combustion analyses, all bufagins have been shown to contain an average of about 70 per cent carbon and 8 per cent hydrogen, while all bufotoxins are composed on an average of approximately 62 per cent carbon, 8 per cent hydrogen and 7 per cent nitrogen. Since the molecular weights of bufotoxins vary, their provisional formulas are thus not the same throughout.

Vulpian[6] has been credited with the discovery that the toad is resistant to its own poison, as well as to the action of digitalis. It has since become known that it is also tolerant to other members of the digitalis group.[7] Chen and Chen[8] have demonstrated that the tolerance of the toad toward digitaloid glycosides is essentially that of the cardiac muscle. Working with strophanthin, Epstein[9] arrived at a similar conclusion, i.e. that the resistance of the toad is due to the resistance of the

heart muscle. Chen and Chen have also shown that the toad's heart is equally resistant to bufotoxins and bufagins and concluded that this is due to the fact that the latter substances have a digitalis-like action.

Chen and Chen[5] have carried out extensive pharmacological studies on toad poisons, demonstrating an effect on the heart very similar to that of cardio-active drugs. On perfusion through the inferior vena cava in frogs with appropriate concentrations, the authors have shown a decrease in heart rate, partial A-V block and even complete auriculo-ventricular dissociation, and finally a systolic standstill. In anesthetized cats and dogs a slow intravenous injection of a dilute solution of these substances resulted in cardiac slowing, arrhythmias and cardiac collapse. Electrocardiograms recorded from etherized cats revealed prolongation of the P-R interval, bradycardia, ectopic beats, and ventricular fibrillation. Double vagotomy eliminated prolongation of the P-R interval and tended to increase the toxicity of these substances in the majority of experimental animals. Also following administration of atropine these principles have no longer any influence on A-V conduction or cardiac rate. The authors concluded that the mode of action was through the vagal centers or vagal endings and directly on the myocardium. The arterial blood pressure was found to be raised promptly by lethal or sub-lethal doses. The emetic action (one of the cardinal toxic effects of all cardiac glycosides) was also demonstrated.

By using Hatcher's method of investigation, Chen and Chen[5] have determined the persistence of action of these substances. They found that from 30 to 70 per cent of the cat unit of the majority of the compounds are eliminated in one to six hours. The persistency of action has already been mentioned to be possibly dependent upon the presence of the sugar groups in the cardio-active moiety. It is because the active principles of the toad poisons lack this property which constitutes such an important factor in cardiac therapy that they appear to possess little therapeutic value as compared with other heart remedies. This is fortunate, as the commercial preparation of such animal products presents obvious difficulties, while the cultivation of various plants can easily be expanded whenever their value in therapy is demonstrated.

Erythrophleine

It is interesting to know that in addition to cardiac glycosides so far discussed in this text, a cardio-active principle which is not a glycoside but an alkaloid has been obtained from the bark of Erythrophloeum guineense. The bark is known by a number of common names such as

sassy, mancona, or red-water tree bark. It has long been employed by the natives of Western Africa as an ordeal in their trials for witchcraft and sorcery. It appears that the bark has been first chemically examined by Gallois and Hardy,[10] who succeeded in isolating from it a toxic alkaloid which they named erythrophleine. This substance has been found by Harnack[11] to possess the empiric formula $C_{28}H_{43}O_7N$ or $C_{28}H_{45}O_7N$. However, somewhat varying results have been obtained by different investigators. This may be attributed to the use of barks from different species of Erythrophloeum. Harnack has found that the substance produced digitalis-like effect in both cold-blooded and warm-blooded animals. Power and Salway,[12] on administering an alcoholic extract of the bark to dogs, have observed vomiting and slowing of the heart rate. Intravenous administration of the commercial erythrophleine hydrochloride to rabbits also resulted in cardiac slowing.

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Conclusions

THERAPY may be symptomatic, specific, or curative. Thus morphine suppresses consciousness of pain, insulin acts specifically on hyperglycemia, and penicillin cures by eliminating the infectious agent. Digitalis falls into the group of non-curative specific medications which remove symptoms by altering the underlying functional defect, without effecting the causative agent or organic lesion. Cardiotonic drugs bring relief, may prolong life, and temporarily restore a patient to more active and useful status. At the same time the diseased heart is not restored to a healthy state. However, its performance is improved by an alteration in biochemical processes, the salutary change being brought about by the drug in some still mysterious fashion.

Nature has provided the therapeutic enthusiast with plentiful sources of cardiac remedies. The reader by now is only too conscious of the many different species of plants found to contain the useful cardiac principles. Of the numerous sources, comparatively few have been utilized for the preparation of drugs. However, from the point of view of the practicing physician, even these few may be too many. The market has been flooded with a great number of different products of commerce. Among preparations from the whole leaf of Digitalis purpurea, in addition to official digitalis, there are available digifolin, digalen, digipoten, digitan, digitol, and French digitalin. From the seeds of the same plant – German digitalin. From the whole leaf of Digitalis lanata – digilanid. In addition, there are many preparations containing one or two glycosides, such as digitoxin, digitaline Nativelle, digoxin, gitalin (amorphous), lanatoside C, various strophanthins, scillaren, urginin, and thevetin. When confronted with the problem of treating a patient in heart failure, which drug is the physician to choose?

The choice of the drug will depend to a large extent upon the method of administration. As long as oral medication is most commonly employed and is entirely satisfactory in the great majority of cases, the whole leaf of digitalis will continue to render its valuable services. The official digitalis, however, is not by any means the only useful drug that can serve this purpose. Preparations from the whole leaf of Digitalis lanata are equally satisfactory and in addition possess the advantages of relative chemical purity and known constant composition. Other products possess similar advantages. The nearly complete absorption from the digestive tract of digitoxin (digitaline Nativelle), which at the same time appears to be nearly devoid of any irritating properties, allows a prompt attainment of full therapeutic effect with a single digitalizing dose. This is hardly possible with official digitalis because of poorer absorbability and gastro-intestinal irritation by local action produced by massive doses administered at once. Lanatoside C is also a useful drug although the question remains as to whether or not its oral administration may be more efficacious than in the case of ordinary digitalis.

In instances where rapid digitalization by intravenous route is deemed advisable, the older preparations of digitalis are no longer acceptable. Purified glycosidal substances exclusively are to be used for that purpose. Strophanthin ranks high, but its use should be restricted to cardiologists or to large hospital services where it can be employed under close supervision by competent and experienced physicians. The reasons for this caution have already been given in the appropriate chapter. For general use lanatoside C is a valuable drug. In rapidity of action it approaches strophanthin. Digitoxin and digoxin will also be found useful under similar circumstances.

On intravenous administration of any cardiotonic principle great caution should be exercised. Before giving a patient a single full digitalizing dose one has to make certain that the patient has not recently received any other preparation of digitalis or allied bodies.

With regard to the problem of ordinary digitalis *versus* purified glycosides this much can be said in favor of the latter group of drugs. Although the biological variations from patient to patient in tolerance to and requirements for the drug will always be the most important factor in determining the amount of the medicinal agent to be administered, the other variable, that of the amount of the active principle contained in the individual sample dispensed is eliminated with the use of pure glycosides. For this reason, along with the others men-

tioned in this text, it may be expected that greater reliance will be placed on glycosidal preparations in the future than heretofore. While it is desirable to know the properties of various cardiac drugs, it is not practical to use them all. Instead it is best to become thoroughly familiar with one or two reliable preparations and employ them extensively.

It may be mentioned in passing that during the recent state of emergency, with the scarcity of the available stores of quinidine, more frequently than ever before have digitalis bodies been employed for management of cardiac irregularities, excepting ventricular tachycardia. The results are good enough to justify the use of digitalis. While only a single daily dose of this drug is needed, quinidine must be given at regular intervals three, or preferably four times during the twenty-four hour period. If digitalis fails to prevent or greatly diminish the frequency of attacks, quinidine should be tried. But no longer is the latter drug of first preference for prevention of supraventricular arrhythmias and premature ventricular contractions.

No patient's optimal dosage of digitalis can be predicted; it must be determined by properly controlled administration. The finest praise any internist can ask is the statement, 'he knows how to use digitalis,' for this implies knowledge, experience, and judgment.

APPENDIX I

TABLE X

DOSAGE OF CARDIAC GLYCOSIDES

Glycoside	Digitalizing Dose		Daily Maintenance Dose (Oral)
	Oral	Intravenous	
Cedilanid	6.0 mg. in 48 hrs. 7.5 mg. in 72 hrs.	1.6 mg. or 1.2 mg. followed by 0.4 mg. in 2–4 hrs.	0.5–2.0 mg. (Average 1.5 mg.)
Digilanid	4.0–8.0 mg. in 24–48 hrs. (Average 6.0 mg.)	3.0–6.0 mg.	$\frac{1}{3}$ mg.
Digitoxin	1.0–1.25 mg.	1.0–1.25 mg.	0.05–0.2 mg.
Digoxin	1.0–1.5 mg.	0.75–1.0 mg.	0.5 mg.
Gitalin	6.0 mg.		0.5 mg.
G-Strophanthin (Ouabain)		0.5 mg. (Initial dose of 0.25 mg. repeated in 2 hrs.)	
K-Strophanthin		0.5–0.75 mg. (Initial dose of 0.3–0.5 mg. followed by 0.25 mg. in 6 hrs.)	
Strophosid		1.0 mg.	
Scillaren	9.6–14.4 mg. in 72 hrs.		0.8–1.6 mg.
Scillaren B		1.0–1.75 mg. (In divided doses)	
Urginin	6.5–14.0 mg. in 72 hrs. (Average 9.0 mg.)		0.5–1.5 mg. (Average 0.95 mg.)

APPENDIX II

TABLE XI

COMMERCIALLY AVAILABLE PREPARATIONS OF CARDIAC GLYCOSIDES

Source	Glycoside	Product	Manufacturer
Digitalis purpurea	Mostly crystalline digitoxin	Digitaline Nativelle	E. Fougera & Company
		Purodigin	Wyett Company
		Crystodigin	Eli Lilly & Company
	Amorphous gitalin	Gitalin (amorphous)	Rare Chemicals, Inc.
Digitalis lanata	Lanatoside A, lanatoside B and lanatoside C	Digilanid	Sandoz Chemical Works, Inc.
	Lanatoside C	Cedilanid	Sandoz Chemical Works, Inc.
	Crystalline digoxin	Digoxin	Burroughs Wellcome & Co., Inc.
Strophanthus kombé	Amorphous mixture of K-strophanthin — β and cymarin	K-Strophanthin	Abbott Laboratories Burroughs Wellcome & Co., Inc.
	Crystalline K-strophanthoside	Strophosid	Sandoz Chemical Works, Inc.
Strophanthus gratus	Crystalline G-strophanthin	Ouabain	Eli Lilly and Co. Carroll Dunham Smith Phar. Co. Hynson, Westcott and Dunning
Squill	Mixture of crystalline scillaren A and amorphous scillaren B	Scillaren	Sandoz Chemical Works, Inc.
	Amorphous scillaren B soluble	Scillaren B	Sandoz Chemical Works, Inc.
	Mixture of water insoluble urginin A and urginin B	Urginin	Lederle Laboratories, Inc.

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